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Correlation Study of OSA patients using lateral cephalometry and drug-induced-sleep-endoscopy (DISE)

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Correlation Study of OSA patients using Lateral Cephalometry and Drug-Induced-Sleep-Endoscopy (DISE)

by

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THESIS

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ABSTRACT

Correlation Study of OSA patients using lateral cephalometry and drug-induced-sleep-endoscopy (DISE)

Sooyoun Chung, D.D.S.

The aim of the study was to investigate the association between a cephalometric analysis and an endoscopic analysis under sedatives, defined as drug-induced-sleep-endoscopy (DISE). This prospective cross-sectional study included 69 subjects with OSA diagnosed by an overnight sleep study. Lateral cephalogram and DISE were performed on all subjects. Each cephalogram was digitized to examine the craniofacial morphology and airway characteristics of the subjects. Another investigator, an ENT specialist, administered the DISE and determined the location and degree of airway obstruction and the primary structure contributing to airway obstruction. Certain craniofacial structures were distinctive for the OSA subjects including the cranio-cervical angle. The location of obstruction was correlated well between cephalometric analysis and DISE. Although static and two-dimensional, a lateral cephalogram taken during a routine orthodontic examination can help identify a patient who may have an undiagnosed OSA that should be referred for further evaluation by an ENT specialist.

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INTRODUCTION

Obstructive Sleep Apnea

Overview

Obstructive Sleep Apnea (OSA) is a relatively common sleep disorder characterized by recurrent episodes of partial or complete collapse of the upper airway during sleep.[1] Apnea refers to a complete cessation of airflow for at least ten seconds, whereas hypopnea refers to 50% reduction in oronasal airflow associated with either a reduction in oxyhemoglobin saturation or an arousal from sleep.[2]

Apnea-hypopnea index (AHI) is the standard measure of OSA severity, and it is defined by the total number of apneas and hypopneas per hour of sleep. Table 1 shows the breakdown of OSA severity, with commonly-used cut points. [3]

Table 1. Breakdown of OSA severity

Degree of OSA	*AHI*
Normal	0–4
Mild	5–15
Moderate	15–30
Severe	>30

Epidemiology

A population-based study suggested a prevalence of OSA of 4% in middle-aged men and 2% in middle-aged women.[4] It has also been shown that the prevalence is dramatically increased in sub-populations, such as 62% in elderly, 30% in patients with hypertension, 50% in patient with coronary disease, and 71 to 77% in preoperative bariatric surgery patients.[5] OSA affects an estimated 18 million Americans.[6] The annual cost associated with untreated sleep disorders is estimated to be $3.4 billion.[7]

Risk Factors

Risk factors of OSA include, but are not confined to, older age, obesity, male sex, ethnicity, craniofacial morphology, smoking, and alcohol consumption. In the male, prevalence of OSA increases steadily, then reaches a plateau after 60 years of age.[4] For women, prevalence is the lowest in pre-menopausal women at 0.6%, intermediate (1.1%) in post-menopausal women with hormone replacement therapy, but relatively high at 5.5% in post-menopausal women without hormone replacement therapy.[8] One study by Young found that 58% of moderate to severe OSA cases had a body mass index (BMI) of equal or greater than 25 kg/m^2.[9] The same study also pointed out that neck circumferences of greater than 17 inches in male and 16 inches in female were associated with higher risk of developing OSA. In a longitudinal study done by Peppard *et al.*, in 2000, they showed that a 10% weight gain was associated with a 6-fold increase in risk for development of OSA in a 4-year follow up period, whereas a 10% weight loss was associated with a 26% decrease in AHI.[10] The prevalence of moderate to severe OSA among males is estimated 2.5 times higher as for females. [4] African Americans seem to have a higher prevalence of OSA compared to Caucasians.[11] Asian populations have a similar prevalence as Caucasians, although the severity of OSA is higher and with less of a role for obesity.[12] According to Lam *et al.*, certain craniofacial structures are associated with severe OSA in the Asian population, such as an increased thyromental angle and a shorter thyromental distance[12]. Smoking is associated with a higher prevalence of snoring and OSA.[13-16] Even second-hand smoke has been independently linked to habitual snoring.[17] According to Franklin *et al.*, airway inflammation and damage due to cigarette smoke seem to alter the mechanical and neural properties of the upper airway and increase its collapsibility during sleep. This is supported since former smokers do not manifest the increased risk for OSA once they quit.[17] Alcohol also plays a role. Alcohol ingestion can prolong apnea duration and worsen the severity of associated hypoxemia in OSA patients.[18-20] Alcohol can also induce apneic activity in normal or asymptomatic individuals.[18, 21, 22] Epidemiologic data are inconclusive regarding the effects of chronic alcohol use on OSA risk.[1]

Clinical Impacts

Gottlieb *et al.* found out that daytime sleepiness is linearly correlated with severity of RDI.[23] Patients with OSA are 2 to 7 times more likely to have a motor vehicle crash compared to control subjects.[24] They also tend to suffer from psychological conditions such as depression or anxiety.

Besides the unfavorable effects on quality of life, including headaches, memory loss, poor work performance, impaired social interactions, sexual dysfunction, and cognitive performance, OSA also demonstrated strong associations with cardiovascular disease, including hypertension, coronary artery disease, myocardial infarction, congestive heart failure, and cerebrovascular accident.[1] Grote *et al.* studied 1190 consecutive patients referred to the sleep clinic and found out that odds of hypertension with an AHI greater than 40 was four times the odds for an AHI < 5.[25] OSA has been shown to increase the risk of developing type 2 diabetes. It has been shown that intermittent hypoxia, which is a cardinal symptom of OSA, decreased whole-body insulin sensitivity and muscle glucose utilization with no change in hepatic glucose output.[26] Premature death in the 4^{th} and 5^{th} decades of life has been shown to be related to OSA.[1]

Treatment

While there is no cure for this deadly disease, there are many options to manage the condition. Behavioral management includes quitting smoking and alcohol, positional therapy involving avoidance of the supine sleep position, and weight loss. Along with behavioral management, more advanced treatment options include positive airway pressure (PAP), with the most common technologies using continuous PAP (CPAP), mandibular repositioning appliances, and various surgical interventions. PAP is considered the first-line treatment for moderate to severe OSA because it has demonstrated the highest efficacy. PAP functions as a pneumatic splint to prevent upper airway obstruction. Unfortunately, the effectiveness of PAP is limited by compliance, and approximately 50% of OSA patients are unable to tolerate PAP.[27] Mandibular repositioning appliances appear to improve OSA primarily by advancing the mandible and can be highly effective for many patients.[28] Surgical interventions encompass a broad spectrum of procedures, ranging from minimally invasive nasal procedures to more-invasive treatments such as maxillomandibular advancement.[29]

Diagnosis

Airway obstruction in OSA can occur at many levels, and the principal regions of dynamic obstruction are the palate and the so-called hypopharynx (actually corresponding to the hypopharynx and the retrolingual portion of the oropharynx).[30] Successful surgical treatment depends on the accurate diagnosis of the region(s) involved in airway obstruction during sleep for a given patient. For example, uvulopalatopharyngoplasty, a surgical procedure that addresses palatal obstruction, achieves a notable reduction in OSA severity in 54% of cases with primarily palatal obstruction but only in 5% of cases when there appears to be at least some component of obstruction in the hypopharynx.[31] The authors of a major OSA surgery literature review wrote that, "the failure to identify and treat all levels of airway obstruction was the principal factor in surgical treatment failure." A recent Cochrane Collaboration evidence-based medicine review of surgical treatment for OSA expressed the sentiment that determination of the site of obstruction should be a major focus of research efforts in sleep-disordered breathing.[32]

Methods of evaluation commonly used to characterize the pattern of obstruction are clinical examination, awake fiberoptic examination with Muller maneuver, lateral cephalometry, computed tomography (CT), and magnetic resonance imaging (MRI). No single evaluation method has been proven to be ideal, but each may provide valuable information to guide diagnosis and treatment of OSA.

Lateral Cephalometry and OSA

Use in Sleep Field

Lateral cephalometry has become one of the standard diagnostic tools in patients with sleep disorders, especially with regard to the evaluation of the skeletal craniofacial morphology. Not specifically developed for the field of sleep disorders, imaging techniques and standards for data analysis have been incorporated from the field of orthodontics or maxillofacial surgery.

Diagnostic Use: Differentiation Tool

To be a useful diagnostic tool, a method should be able to differentiate patients from healthy controls. Extensive literature is available comparing upper airway anatomy and dentofacial structures using cephalometry between OSA patients and healthy controls, both for obese and non-obese patients as well as for different ethnicities.[33] Reported differences for the OSA patients were a longer soft palate[34, 35], reduced minimum palatal airway widths[34], increased thickness of the soft palate[35-38], increased pharyngeal length[35], retrognathia[38, 39], retroposition of the maxilla[40, 41], increased cranio-cervical angle[42], micrognathia[43], and differences in hyoid bone position[35, 36, 39-41, 43-45]. Ingman *et al.* reported no differences in naso- and hypopharyngeal soft tissues but a significant narrowing on the velopharyngeal level.[46] Tangugsorn *et al.* reported more pronounced aberrations of the cervico-craniofacial structures in non-obese patients, while obese patients had more abnormalities in the upper airway soft tissue morphology, head posture, and the position of the hyoid bone.[47]

Diagnostic Use: Correlation to Severity

In a recent investigation, Hou *et al.* reported that the aberrations in craniofacial morphology were more pronounced in patients with severe OSA in their group of Chinese patients.[48] Yucel *et al.* demonstrated that differences in hyoid bone position and soft palate thickness were more frequent in the subgroup of patients with severe OSA[49]. Many more authors have consistently found out that hyoid bone position is highly correlated with severity of OSA: the more inferiorly positioned the hyoid bone is, the more severe the OSA[50-52]. However, Rose *et al.* question the diagnostic relevance of X-ray cephalometry for OSA, as they found no direct correlation between skeletal cephalometric findings and OSA severity. However, they did report a correlation with hyoid bone position.[53]

In addition, cephalometric analysis has been widely used to plan the treatment for these patients and to evaluate the effects of therapeutic intervention such as with oral appliances [54] and maxillomandibular advancement surgery.[55-57]

Summary

Although lateral cephalogram is a static two-dimensional representation of the airway, a dynamic, 3-dimensional structure, there have been differences demonstrated between controls and those with OSA, with certain measurements related to OSA severity. In addition, a lateral cephalogram is routinely taken as a part of beginning records in almost every orthodontist’s office, enabling orthodontists to screen their patients for this deadly condition and triage properly to better serve their patient’s needs.

With this in mind, we evaluated another diagnostic tool that may allow us to evaluate the 3D structures in dynamic condition, drug-induced-sleep-endoscopy.

Drug-Induced-Sleep-Endoscopy and OSA

The commonly-used surgical evaluation techniques are performed during wakefulness, and it is well established that sleep onset and the transitions from non-rapid eye movement (NREM) to rapid eye movement (REM) sleep are associated with marked changes in upper airway physiology; these changes suggest that upper airway evaluations during wakefulness may be of limited accuracy. Borowiecki *et al.* were the first to report their attempts at natural sleep endoscopy, the endoscopic evaluation of the pharynx during natural sleep in 1978.[58] Their work and the work of subsequent groups were limited by the patients' challenges of falling asleep with an endoscope in place, and the technique has been abandoned.

First described in 1991 by Croft and Pringle in the United Kingdom, drug-induced-sleep-endoscopy (DISE) requires the pharmacologic induction of unconscious sedation, with placement of a flexible fiberoptic telescope to visualize the upper airway.[59] Various pharmacologic agents have been used to perform DISE, including propofol and/or short-acting benzodiazepines, with the former used most commonly. It remains unclear how closely unconscious sedation approximates natural sleep, as sedation produces decreases in muscle tone that may be particularly important in OSA. However, recent evidence suggests that while unconscious sedation under propofol may not be a perfect simulation of natural sleep, with identical effects on upper airway collapsibility, pharyngeal dilator muscle activity appears to lie somewhere between NREM and REM sleep. Under conditions of propofol unconscious sedation, normal subjects have demonstrated decreases in genioglossus tone (as a measurable gauge of upper airway muscle tone) to approximately 10% of maximum awake activity (including tonic and phasic activity),[60, 61] which is approximately one-half to one-third of the level seen at sleep onset in normal subjects [62], but greater than that seen during REM sleep in normal and OSA subjects.[63]

Multiple studies have demonstrated the validity of DISE. Under propofol sedation, all patients with sleep disordered breathing (primary snoring or obstructive sleep apnea) during natural sleep developed sleep disordered breathing under propofol sedation, whereas no control patients developed snoring or disordered breathing.[64] Another study showed greater degrees of collapsibility during DISE with propofol in subjects with OSA compared to those with snoring but no OSA; in the former group, there was a correlation between the apnea-hypopnea index during natural sleep and the degree of tongue region obstruction during DISE.[65]

One of the significant findings achieved using this technique is that obstruction occurs in multiple sites. Abdullah *et al.* found that a combination of as many as five different concomitant sites of obstruction in primary snorers and even six in sleep apnea patients.[66] An isolated site of obstruction was found in only 15% of the OSA patients in the same study. As for the patterns of obstructions, they were described as being circular, antero-posterior, and latero-lateral at the level of the soft palate, the tonsils, the tongue base and the epiglottis.[66, 67] An involvement of the epiglottis is found in less than 1% to as high as 40%.[65-68] Pringle and Croft compared their results of the

Mueller maneuver to those obtained by DISE in a group of 50 patients.[59] Based on the Mueller maneuver, 25 patients would have been selected for UPPP. However, 11 (44%) of those patients showed a substantial hypopharyngeal collapse under sedation, which would have meant excluding them from UPPP. The authors concluded that UPPP would be suitable for patients whose airway obstruction is restricted to the velopharyngeal area, but not for patient whose obstruction pattern is either multisegmental or restricted to the hypopharyngeal region. Stuck and Maurer found that DISE is particularly helpful in detecting or excluding a possible glottis or supraglottic obstruction most often described as a posterior movement of the epiglottis during inspiration.[33] In 27 adult patients with epiglottic collapse during DISE, Golz *et al.* found a statistically significant reduction of the AHI in 85% of patients after partial epiglottectomy.[69] DISE seems to be particularly helpful in cases of laryngeal collapse and failures of standard therapy. No prospective data is available to date comparing success rates of surgical intervention with and without the use of DISE. It would be of particular interest to find out whether surgical outcome correlates to the results of DISE in the future.

PURPOSE

Lateral cephalometry and DISE are two of the most commonly used methods to diagnose patients with OSA. The purpose of this study is to see if the findings of these two methods are correlated.

SPECIFIC AIMS

Specifically I would like to find out if

1. patients with OSA have distinctive craniofacial and/or airway structures compared to population means.
2. any craniofacial structures can be a predictor for airway constriction in naso-, oro- or the hypopharynx.
3. there are any relationships between lateral cephalometric data and those of DISE.

NULL HYPOTHESES

1. The craniofacial and/or airway structures of OSA patients are not different from those of population means.
2. Craniofacial structures do not predict airway constriction at any level.
3. There are not any relationships between lateral cephalometric data and those of DISE.

MATERIALS AND METHODS

Subjects

This prospective cross-sectional study included 71 patients seen at the University of California, San Francisco Department of Otolaryngology—Head and Neck Surgery. Inclusion criteria were the following: age > 18 years, apnea-hypopnea index (AHI) > 5 diagnosed by overnight sleep study, unable to tolerate positive airway pressure therapy, and elected to proceed with surgical treatment. Exclusion criteria included: pregnant women and any contraindication to the use of propofol such as allergy. This study was approved by the University of California, San Francisco institutional review board.

71 patients underwent DISE (Drug-Induced-Sleep-Endoscopy) and lateral cephalogram. Two subjects were excluded from this study due to the poor quality of the lateral cephalograms, leaving 69 patients for evaluation (Table 2). 7 of the patients were female, and 62 of the patients were male.

Table 2. Demographic information of 69 subjects

	Mean	S.D.	Range
age	43.4	9.5	20.0 – 66.7
BMI	30.2	4.6	22.0 – 42.4
AHI	43.6	25.0	8.7 - 120

Lateral Cephalometry

Lateral cephalograms of 47 subjects were taken at the University of California, San Francisco, Oral Radiology Clinic in the Dental School, using Kodak 8000C (78kV, 12mA). 22 lateral cephalograms were taken in various dental imaging laboratories throughout northern California, using standardized cephalostat machine settings.

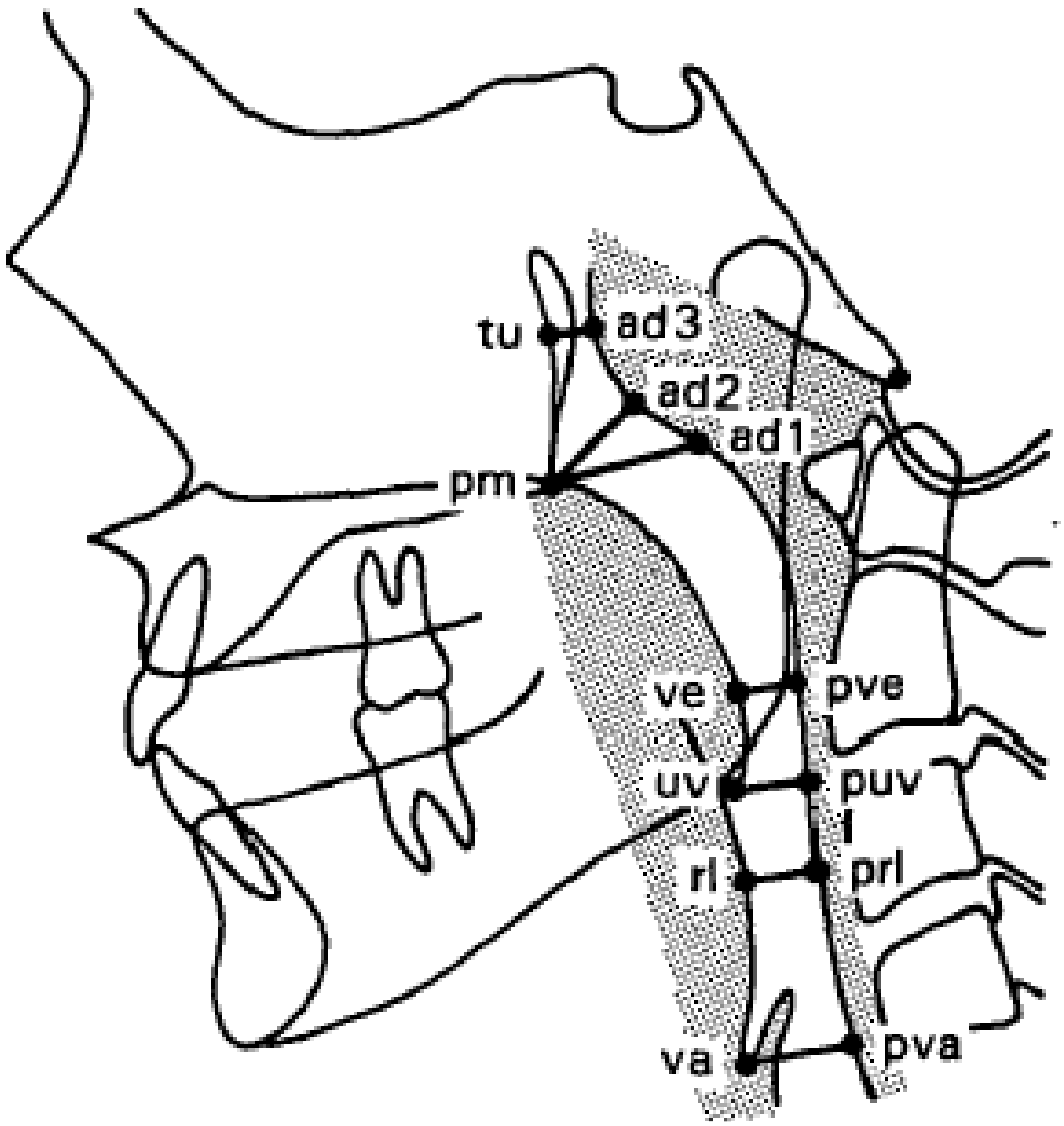
Tracing

All 69 lateral cephalograms were scanned and uploaded to TIOPS program (Copenhagen, Denmark). Brightness and contrast were adjusted to facilitate the best landmark identification process.

'AirwayMes', a new regimen was created to facilitate airway analysis. This regimen includes 11 landmarks to measure airway size anteroposteriorly in naso-, oro-, and hypopharynx in addition to traditional landmarks used in routine orthodontics (Figure 1). It also includes four landmarks located in second and fourth cervical vertebrae to characterize the head posture of these subjects (Figure 2). A total of 79 landmarks were identified on each film, unless the hyoid bone was not captured in the film. The comprehensive list of landmarks used in the study are described and illustrated in Table 3 and Figure 4, respectively.

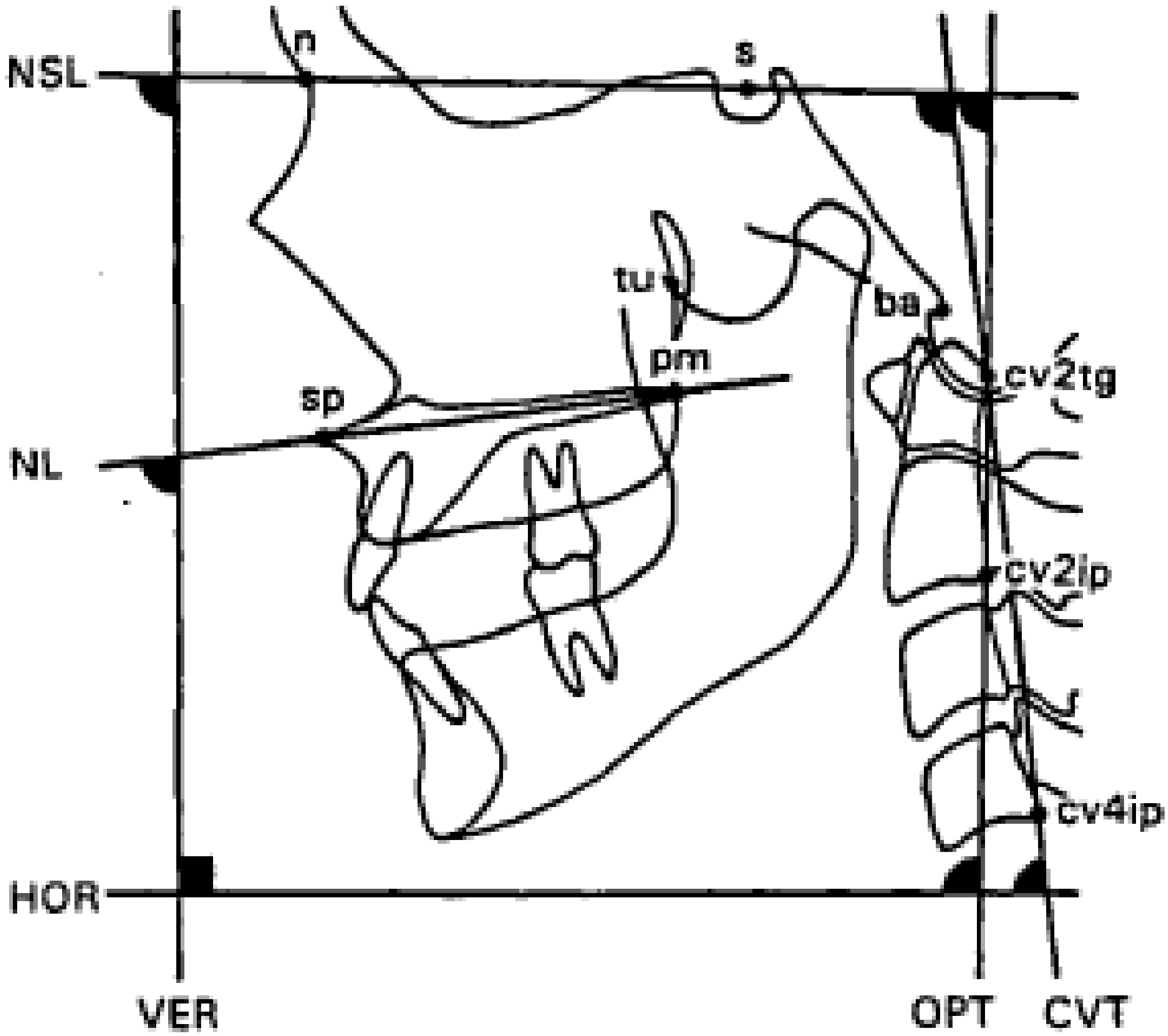
Once the digitization was completed by the principal examiner, all the digitized points were verified by a committee member who has expertise on lateral cephalometry. To eliminate possible bias from occurring while examining these patients, both the examiner and the committee member were blind to the medical history or physical exam findings, sleep study results, or planned procedures at the time of tracing.

Figure 1. Seven airway dimensions



B. Solow *et al.* Eur J Orthod 18 **1996**:571-579

Figure 2. Landmarks for head posture



B. Solow *et al.* Eur J Orthod 18 **1996**:571-579

Table 3. Landmarks used in the analysis

Lateral Landmarks	Eur Amer	Definitions
Nasion	n	Anteriormost point of the frontonasal suture
SellaAnterior	sa	Intersection of the anterior contour of sella turcica and the NSL
Sella	s	Center of Sella Turcica
Basion	ba	Most postero-inferior point on the anterior margin of foramen magnum
SecondCervicalVertebraApex	scap	Apex of the odontoid process of the second cervical vertebra
SecondCervicalVertebraTangent	sctg	Tangent point of the CVT of the odontoid process of the second cervical vertebra
SecondCervicalVertebraInf	scip	Most inferio-posterior point of the corpus of the second cervical vertebra
FourthCervicalVertevraInf	fcip	Most inferio-posterior point of the corpus of the fourth cervical vertebra
Nasal Apex	na	Tip of nasal bone
Articulare	ar	Intersection of the external contour of the cranial base and the posterior contour of the condyle
RamusLine Sup	rls	Deepest point of the posterior contour of the mandibular ramus
RamusLineInf	rli	Tangent point to the posterior contour of the mandibular ramus through the ar
Gonion	go	Intersection of the gonial contour and a line dividing the angle between the ML and RL
Mandibular Line Post	mlp	Tangent point to the inferior contour of the mandible through gn

Antegonion	ag	Superiormost point of the antegonial notch in relation to ML
Mandibular Line Ant	mla	Tangent point of the inferior contour of the mandible through mlp
Supramentale	sm Bpoint	Posteriormost point of the anterior contour of the mandibular symphysis/lower alveolar process
Suprapogonian	spg	Tangent point to the anterior contour of the mandibular symphysis through sm
Pogonion	pg	Tangent point the anterior contour of the mandibular symphysis through n
Prognathion	pgn	Point on the mandibular symphysis at the greatest distance from the cd
Gnathion	gn	Inferiormost point of the mandibular symphysis
Symphyseon	sym	Posteriormost point of the mandibular symphysis
Mandibular Ref 1	ma 1	Mandibular reference point 1 - Anterior
Mandibular Ref 2	ma 2	Mandibular reference point 2 – Posterior ma1/ma2 should be placed on a line through spg
Pterygomaxillare	pm PNS	Intersection point of the nasal floor and posterior contour of the maxilla
Palation	pal	Point where the asi meets the palatal contour when ILs is rotated with center in isi
Subspinale	ss Apoint	Posteriormost point of the anterior contour of the maxilla / the upper alveolar process
Spinalpoint	sp ANS	Apex of anterior nasal spine
Maxillar Ref 1	mx1	Maxilla Reference point 1 - Anterior
Maxillar Ref 2	mx 2	Maxilla Reference point 2 – Posterior: mx1/mx2 should be placed on the line sp-sa
Incisal Inf Incisor	iii	Midpoint of the incisal edge of the most prominent lower incisor

Apex Inf Incisor	aii	Apex of the lower incisor defined by the apex point of the tooth template
Mesial Inf Molar	mim	Mesial contact point of the average lower molar
Root Inf Molar	rim	Root point of the lower molar defined by the root point of the tooth template
Incisal Sup Incisor	isi	Midpoint of the incisal edge of the most prominent upper incisor
Apex Sup Incisor	asi	Apex of the upper incisor defined by the apex point of the tooth template
Mesial Sup Molar	msm	Mesial contact point of the average upper molar
Root Sup Molar	rsm	Root point of the upper molar defined by the root point of the tooth template
BicuspidOccl Point	pop	Cusp tip of the first lower premolar
Frontal Tangent	ft	Frontal tangent point of NFL
SupraGlabellareSoft	sgs	Deepest point of the soft tissue fossa supraglabellaris
Glabella Soft	gs	Anteriormost point on the soft tissue glabella
Nasion Soft	ns	Deepest point in the soft tissue fronto-nasal curvature
DorsumNasi	dn	Point located at the greatest convexity or concavity of the dorsum nasi
Upper Nasal Tangent	rnt	Nasal tangent point of NFL
Pronasale	prn	Prominent most point on the apex of the nose
Lower Nasal Tangent	lnt	Nasal tangent point of NCL-E line
Nasal Septum Tangent	nst	Anterior tangent point of the tangent to the nasal septum through sn
Subnasale	sn	Deepest point of the naso-labial curvature
subspinaleSoft	sss	Dorsalmost point of the upper lip contour
Labrale Sup	ls	Prominent most point on the prolabium of the upper lip
Labrale Sup Tangent	lst	Tangent point to the prolabium of a tangent parallel to the line ls-sts
Stomion Sup	sts	Most antero-inferior point on the prolabium of the upper

		lip
Stomion Inf	sti	Most antero-superior point on the prolabium of the lower lip
Labrale Inf Tangent	lit	Tangent point to the prolabium of a tangent parallel to the line li-sti
Labrale Inf	li	Prominent most point on the prolabium of the lower lip
Lower Labial Tangent	lit	Superior tangent point to the lower lip through sms
Submentale Soft	sms	Deepest point of the mento-labial sulcus
Pogonion Soft	pgs	Tangent point to the anterior contour of the chin through ns
Chin Tangent	ct	Tangent point to the chin of the NCL-E line
Prognathion Soft	pns	Soft tissue point overlying pgn
Gnation Soft	gns	Soft tissue point overlying gn
Submentale	sme	Deepest point in the submental-neck curvature
Hyoideon	hy	Most antero-superior point of the corpus of the hyoid bone
Tuber Maxillare	tu	Posteriormost point of the maxillary tuberosity
Adenoid Prominence 1	ad1	Point at the shortest distance from tu at the pharyngeal adenoid prominence
Adenoid Prominence 2	ad2	Point at the shortest distance from pm at the pharyngeal adenoid prominence
Adenoid Prominence 3	ad3	Point at the intersection of pharyngeal adenoid prominence and line from pm to ba
Post Vellacula epiglottis	pve	The point on the posterior pharyngeal wall closest to ve
Post Uvula	puv	The point on the posterior pharyngeal wall closest to uv
Post Radis Linguae	prl	The point on the posterior pharyngeal wall closest to rl
Post Velum Palati	pva	The point on the posterior pharyngeal wall closest to va
Vallecula epiglottis	va	The most inferior point on the valley of the epiglottis
Radix linguae	rl	The point on the root of the tongue closest to the dorsal pharyngeal wall

uvula	uv	The tip of the uvula of the soft palate
Velum palati	ve	The point on the soft palate closest to the dorsal pharyngeal wall

Figure 3. Illustrations of landmarks used in the analysis

Measurements

22 measurements, 11 angular and 11 linear, were made on each tracing to evaluate and characterize the skeletal, dental and soft tissue profile of each subject (Table 4). 11 linear measurements included nine soft tissue measurements that help to characterize these patients' airway dimensions and propensity to collapse (Table 5). These include three measurements in the nasopharynx: airway1-3, three in the oropharynx: airway 4-6, and one in the hypopharynx. In particular, Airway 4 measures ve-pve, the most constricted airway behind the soft palate, whereas Airway 6 measures rl-prl, the most constricted airway behind the tongue (Figure 1). Two measurements, commonly measured in obstructive sleep apneic patients, soft palate length and the distance between hyoid bone and mandibular plane were also included.

Reliability of Cephalometric Measurements

Ten films were randomly selected and digitized three weeks later to test the intra-examiner reliability. Average tracing of ten films at each time point was generated using the TIOPS program. Each average tracing at the two time points were superimposed to show the agreement of the two different tracings (Figure 4).

95% confidence intervals of each measurement from the two time points were generated to see if they overlap, quantifying intra-examiner reliability.

Table 4. List of 22 measurements used in the analysis

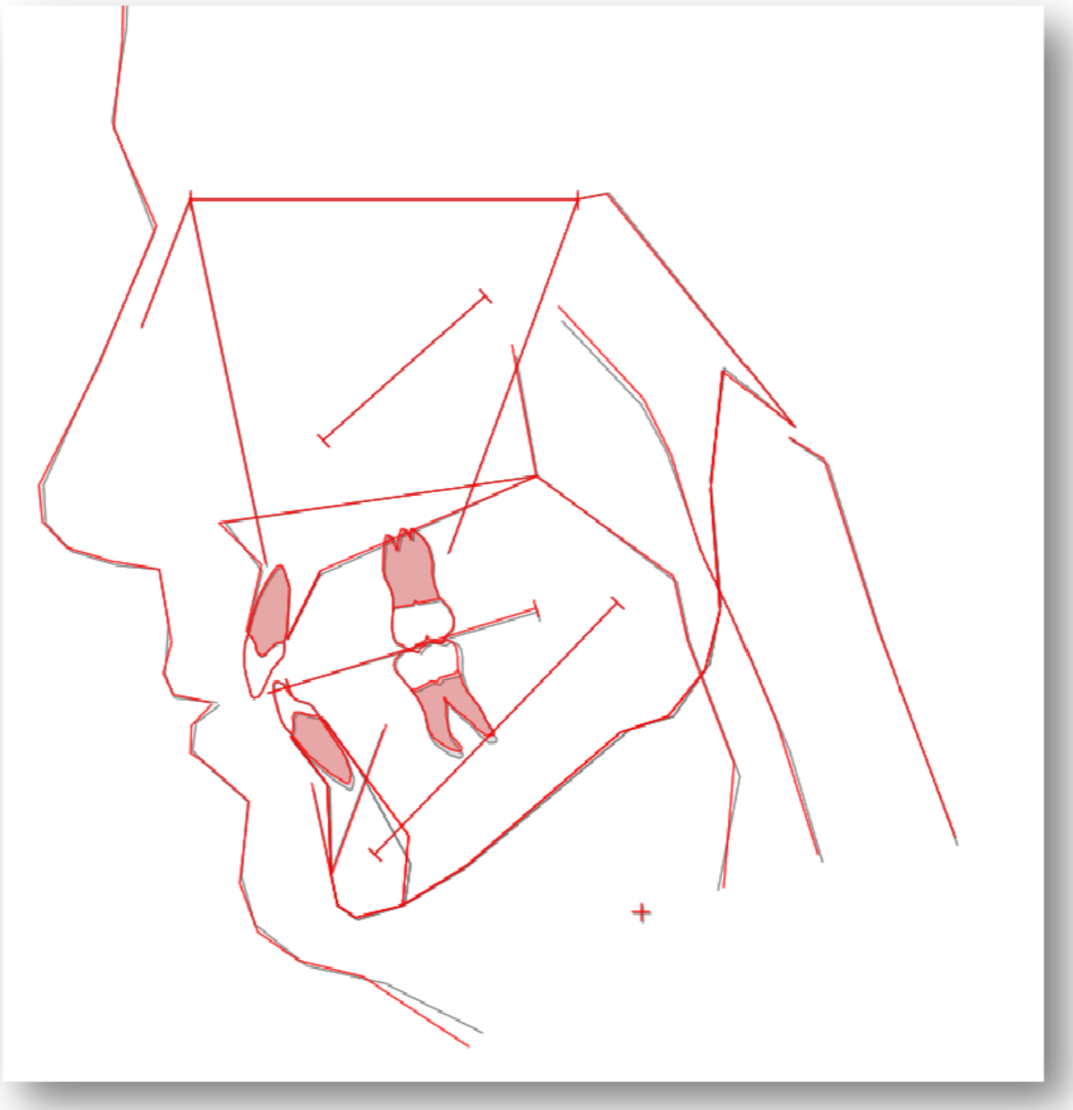
Measurement	**Definition**
SNA	Angle between S-N and N-A
SNB	Angle between S-N and N-B
ANB	Angle between N-A and N-B
OJ	Horizontal distance between labial surface of mandibular incisor to the incisal edge of maxillary incisor
OB	Vertical distance between incisal edge of mandibular incisor to the incisal edge of maxillary incisor
N-S-Ar	Angle between S-N and S-Ar, cranial base angle
N-S-Ba	Angle between S-N and S-Ba, cranial base angle
NSL/OPT	Angle between S-N and tangent line of distosuperior point and distoinferior point of C2
PP/SN	Angle between palatal plane and S-N
MP/SN	Angle between mandibular plane and S-N
PP/MP	Angle between palatal plane and mandibular plane
U1/PP	Maxillary incisor angulation relative to palatal plane
L1/MP	Mandibular incisor angulation relative to the mandibular plane
MP-H	Distance between hyoid bone and mandibular plane
PNS-uvula	Distance between posterior nasal spine to uvula
Airway 1	Uppermost airway dimension in nasopharynx
Airway 2	Middle airway dimension in nasopharynx
Airway 3	The most inferior airway dimension in nasopharynx
Airway 4	The most constricted airway dimension behind the soft palate
Airway 5	The most constricted airway dimension between uvula and posterior pharyngeal wall
Airway 6	The most constricted airway dimension behind the tongue
Airway 7	The most constricted airway dimension between vallecula epiglottis and posterior pharyngeal wall

Table 5. Nine soft tissue measurements

Measurement	Definition
Airway 1 (tu-ad1)	Uppermost airway dimension in nasopharynx
Airway 2 (pm-ad2)	Middle airway dimension in nasopharynx
Airway 3 (pm-ad3)	The most inferior airway dimension in nasopharynx
Airway 4 (ve-pve)	The most constricted airway dimension behind the soft palate
Airway 5 (uv-puv)	The most constricted airway dimension between uvula and posterior pharyngeal wall
Airway 6 (rl-prl)	The most constricted airway dimension behind the tongue
Airway 7 (va-pva)	The most constricted airway dimension between vallecula epiglottis and posterior pharyngeal wall
Soft palate length (PNS-uv)	Distance between posterior nasal spine to uvula
MP-H	Distance between hyoid bone and mandibular plane

Figure 4. Superimposition of tracings at two time points

(grey: average tracing of 10 films at time point 1, red: average tracing of the same 10 films at the time point 2)



Drug-Induced-Sleep-Endoscopy (DISE)

This part of the study was performed and analyzed by a committee member, Eric Kezirian, MD, MPH. Topical decongestant (oxymetazoline 0.05%) was applied to both nasal cavities, and a topical anesthetic/decongestant mixture (3-6mL of 1% lidocaine with 1/100,000 epinephrine) was applied to one nasal cavity. Patients were placed in a supine position on the operating room table with lights dimmed. Oximetry and cardiac rhythms were monitored by the anesthesia team throughout the procedure, and supplemental oxygen was administered by either a facemask or nasal cannula as necessary. An intravenous infusion of propofol was used as the sole agent to achieve a target level of anesthesia. This target level of anesthesia was the minimum level of propofol to achieve drug-induced sleep with arousal to verbal stimulation. With the onset of drug-induced sleep, the flexible fiberoptic laryngoscope was passed through one nasal cavity to perform the examination.

Three analyses were completed. The first analysis evaluated whether there was obstruction at the level of the palate or hypopharynx. The second analysis looked at the degree of palatal and hypopharyngeal obstruction. This was graded separately for each region in an ordinal fashion: <50%, 50-75%, and >75% obstruction. Lastly, the third analysis evaluated each region for specific anatomical structures contributing to the obstruction. Structures were categorized as those at the level of the palate (palate, tonsils when present, and lateral pharyngeal walls at the level of the velopharynx) and the hypopharynx (tongue, epiglottis, and lateral pharyngeal walls at the level of the hypopharynx).

Statistical Analysis

First, to test if the study subjects demonstrated skeletal, dental, and soft tissue morphologies that were different from the general population, descriptive statistics of the cephalometric measurements were calculated and compared to accepted population means using *t*-tests.

Secondly, to test for gender difference, we compared cephalometric measurements between female and male subjects using two-sample t-tests.

Thirdly, to examine if any of the skeletal or dentoalveolar measurements were correlated with airway measurements, soft palate length, and/or hyoid bone position on lateral cephalogram, a Pearson correlation analysis was performed.

To evaluate the potential association between cephalometric measurements and location of airway obstruction (whether palate or hypopharynx), a two-sample t-test compared each measurement from subjects who demonstrate obstruction at the level of palate and from subjects who demonstrate obstruction at hypopharynx level.

To test if the degree of obstruction at the palatal and hypopharyngeal levels during DISE associated with morphology, we compared cephalometric measurements of subjects with moderate (50 to 75%) and severe (more than 75%) obstruction, using separate two-sample t-tests for the two regions. The subjects who demonstrated less than 50% obstruction were excluded from the analysis.

Finally, to examine the potential association between cephalometric measurements and the primary structure contributing to airway obstruction, we compared cephalometric measurements across the various palatal and hypopharyngeal region structures. The structures that were considered at the level of the palate were the palate, tonsils, and lateral pharyngeal walls at the level of palate. The structures that were considered at the level of hypopharynx were the tongue, epiglottis, and lateral pharyngeal walls at the level of the hypopharynx. Two-sample t-tests were performed for pairs of structures within a certain region, e.g. for the hypopharynx, the t-tests compared tongue vs. epiglottis, epiglottis vs. lateral pharyngeal walls, or lateral pharyngeal walls vs. tongue. P values below 0.05 were considered statistically significant.

RESULTS

Reliability of Cephalometric Measurements

In evaluating the intra-observer reliability, the biggest discrepancy between the two tracings in the linear measurements was at Airway 4 (ve-pve), retrolingual airway in the amount of 1.4mm, whereas the biggest angular discrepancy was at ILs/NL, maxillary incisor angulations relative to the palate in the amount of 2.0°.

Normality of the Measurements

Scattergrams and bar graphs were generated with subjects as independent variables and various measurements as dependent variables, including airway 1 to 7, soft palate length, and hyoid bone position relative to mandibular plane to see if the measurements are normally distributed. Upon examination of the shape of the bar distribution, it was determined that the measurements were normally distributed (figure 5 through 14).

Male vs. Female

Female OSA patients showed more mandibular retrognathia compared to males. The mean SNB value of female OSA patients was 75.5 ± 5.4°, whereas it was 79.2 ± 4.6° in male patients ($p < 0.05$). None of the other measurements showed statistically significant difference between genders with p value < 0.05 (Table 6).

Figure 5. Scattergram of soft tissue measurements

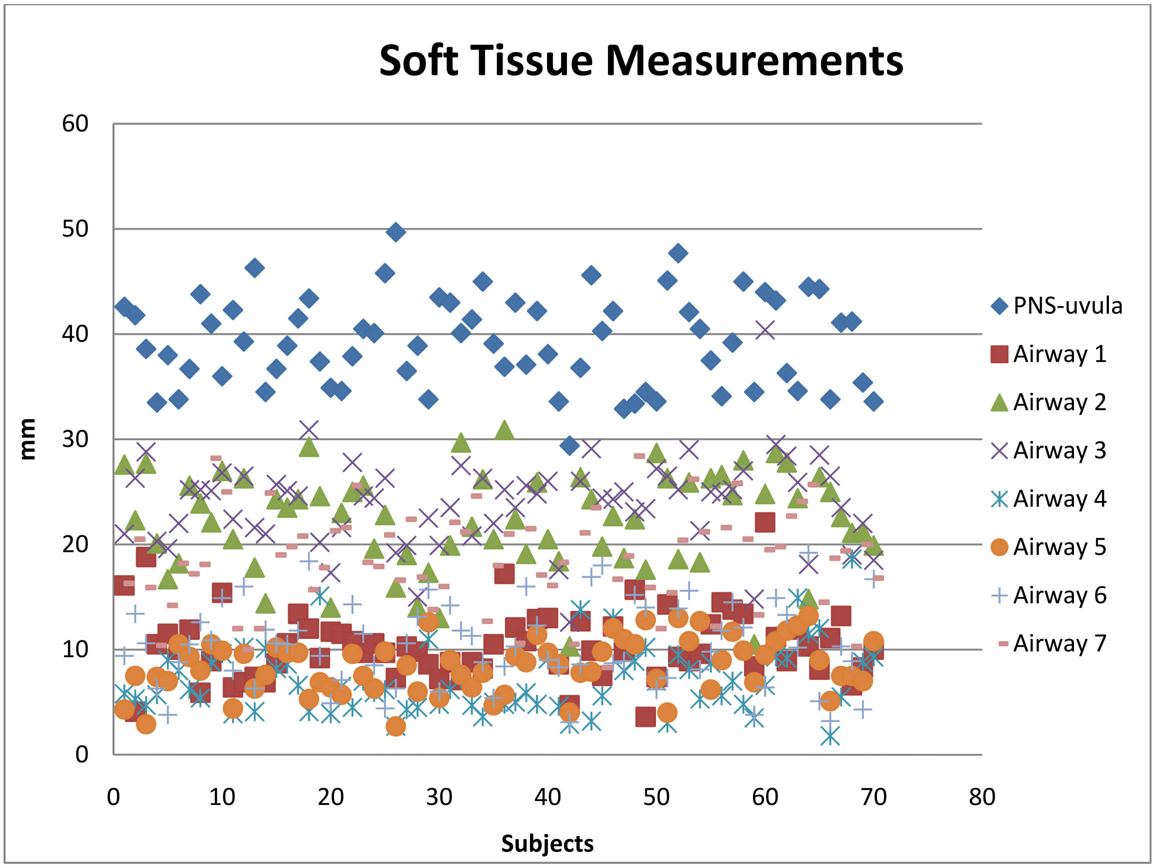


Figure 6. Distribution of Airway 1

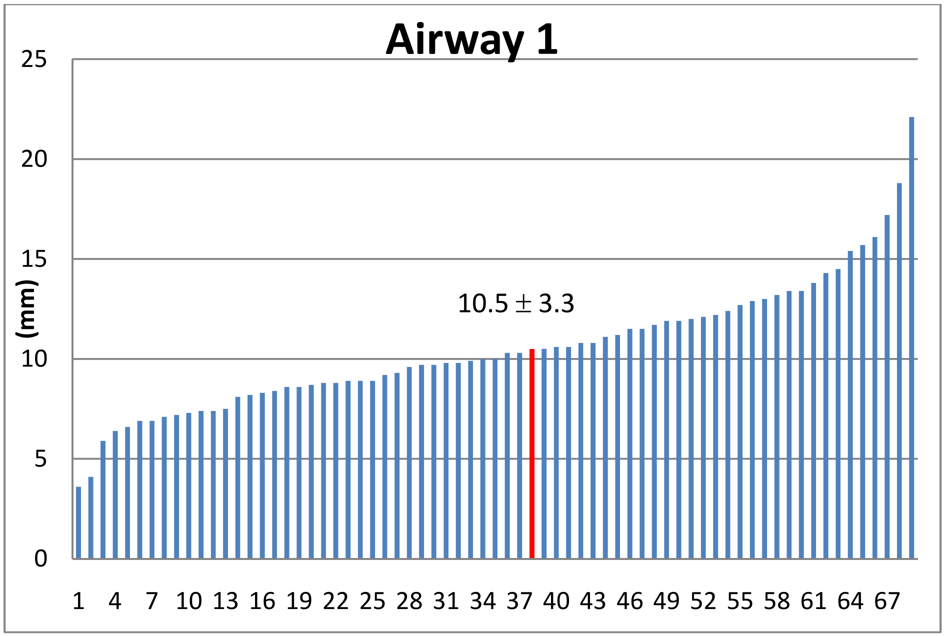


Figure 7. Distribution of Airway 2

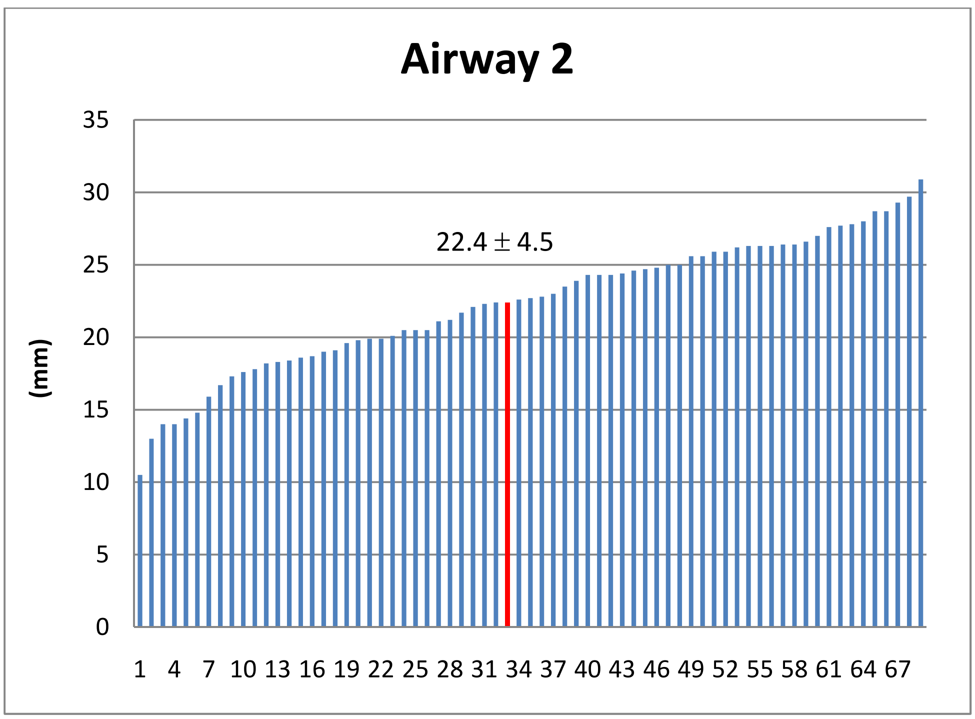


Figure 8. Distribution of Airway 3

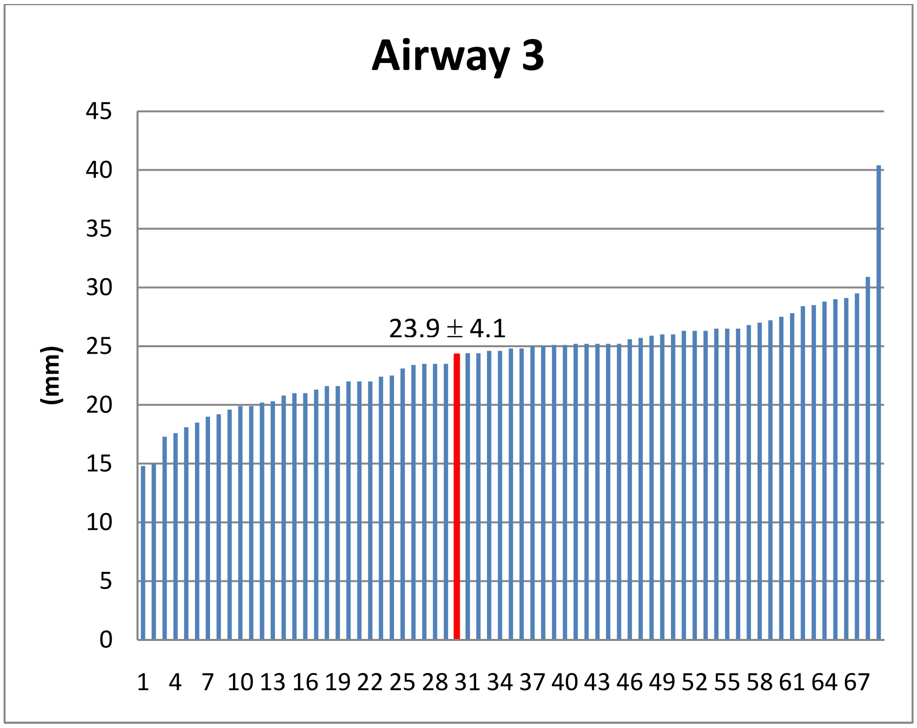


Figure 9. Distribution of Airway 4

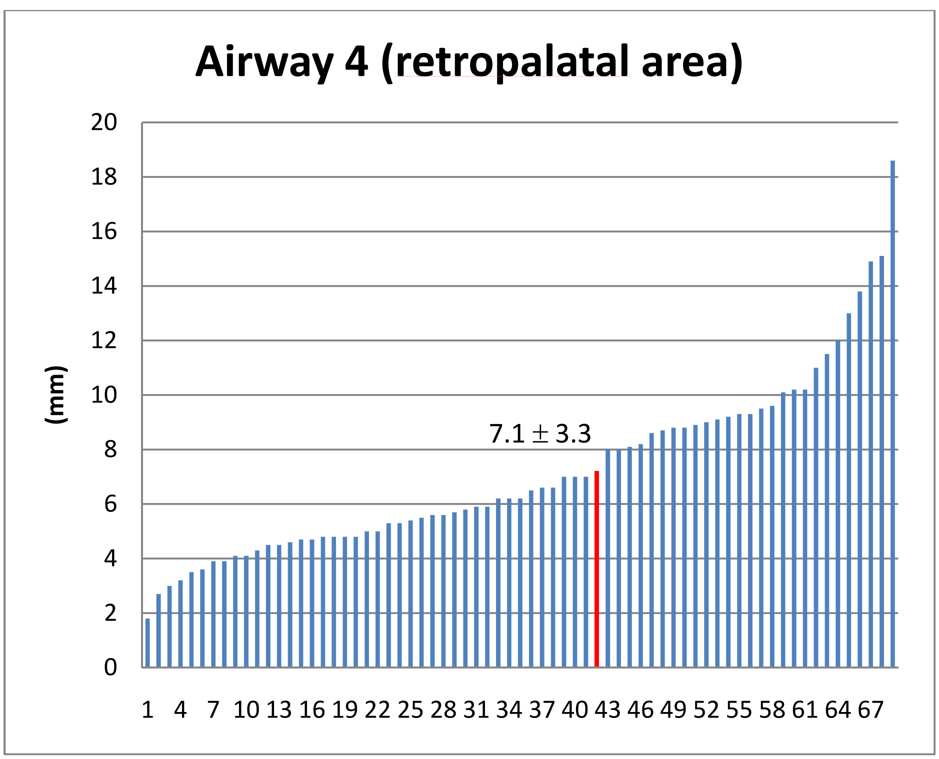


Figure 10. Distribution of Airway 5

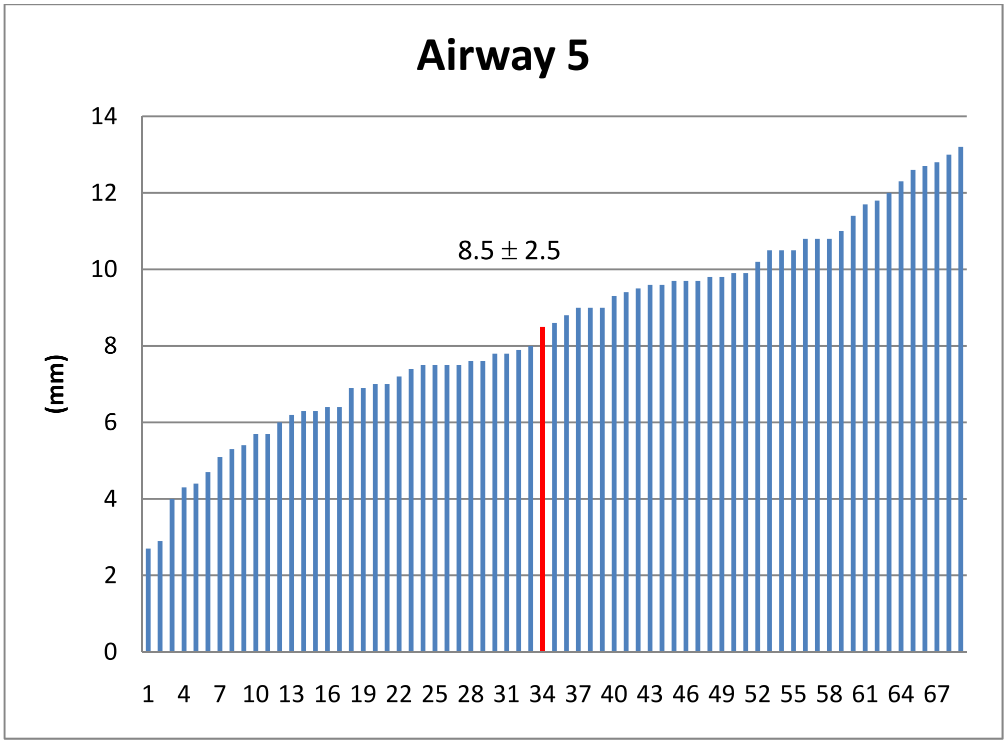


Figure 11. Distribution of Airway 6

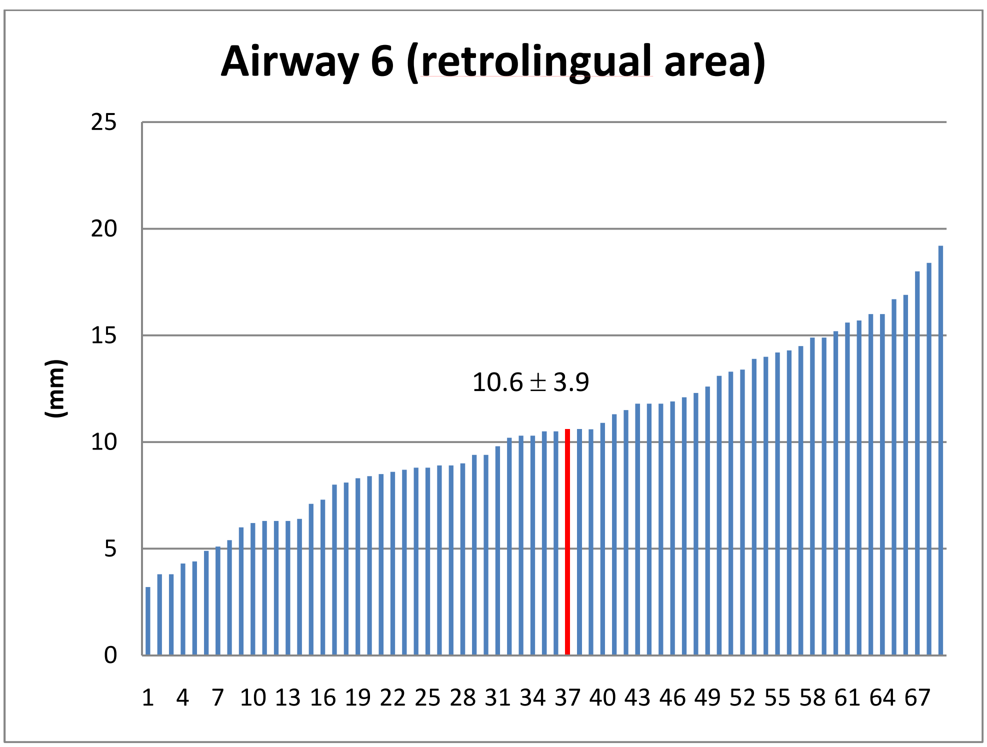


Figure 12. Distribution of Airway 7

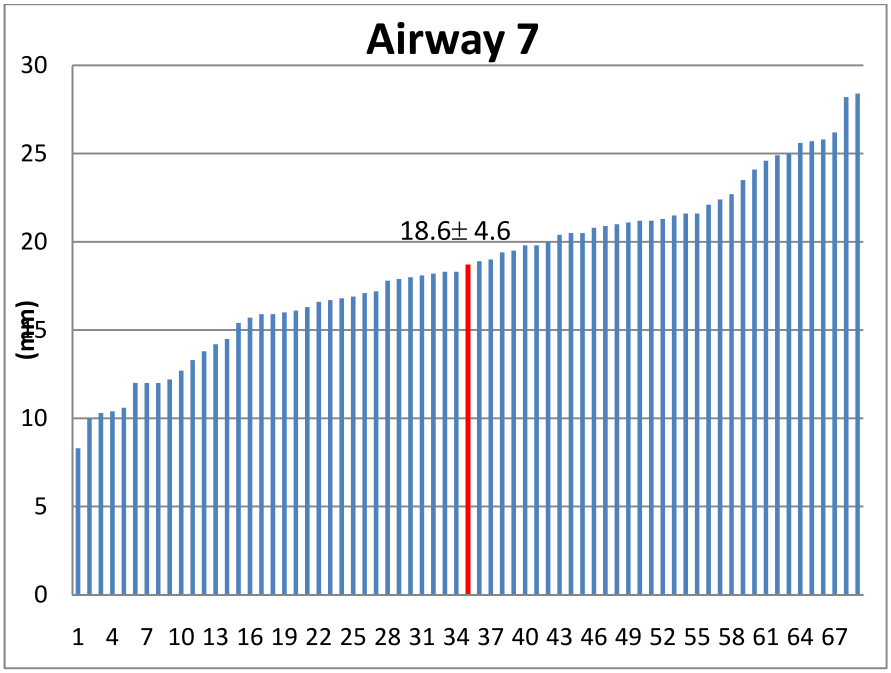


Figure 13. Distribution of Soft Palate Length

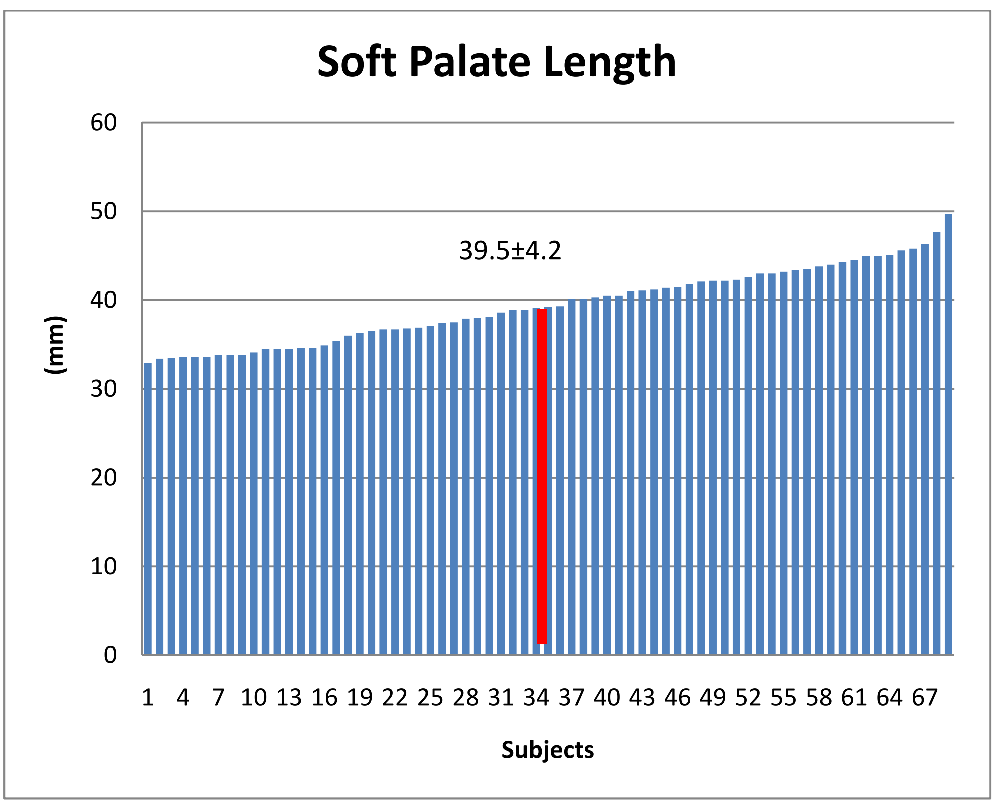


Figure 14. Distribution of MP-Hyoid distance

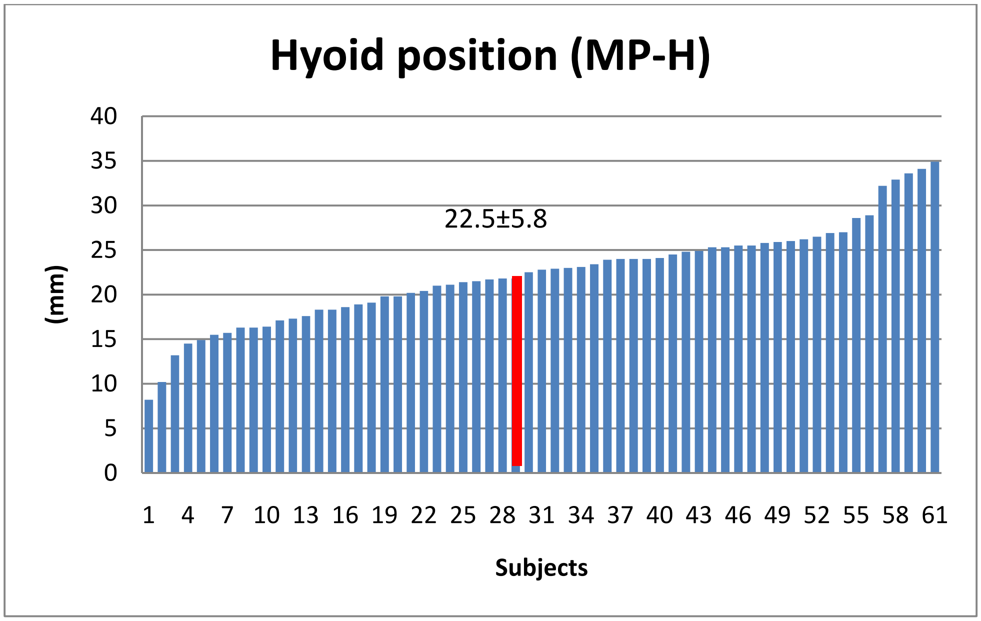


Table 6. Cephalometric Measurements of female *vs.* male OSA patients

	Female (n=7)	Male (n=62)	P value
SNA	79.2 ± 6.3	81.8 ± 4.8	0.1981
SNB	75.5 ± 5.3	79.2 ± 4.6	0.0485*
ANB	3.7 ± 2.5	2.6 ± 2.9	0.3232
PNS-P	37.6 ± 3.7	39.6 ± 4.3	0.2553
MP-H	20.3 ± 3.4	22.8 ± 5.9	0.3314
OJ	3.5 ± 1.4	3.1 ± 1.8	0.6362
OB	2.2 ± 0.9	2.1 ± 2.0	0.9680
NSAr	124.6 ± 6.2	120.0 ± 6.7	0.1257
NSBa	129.7 ± 4.5	125.6 ± 6.0	0.0896
NSL/OPT	111.7 ± 7.0	109.1 ± 7.9	0.4176
PP/SN	8.1 ± 2.8	7.4 ± 3.8	0.6486
MP/SN	36.8 ± 7.2	31.9 ± 6.8	0.0742
PP/MP	28.7 ± 6.1	24.5 ± 5.6	0.0659
U1/PP	106.2 ± 11.3	110.2 ± 6.2	0.1408
L1/MP	94.7 ± 5.2	92.9 ± 7.0	0.5131
Airway 1	11.1 ± 2.2	10.4 ± 3.4	0.5891
Airway 2	21.7 ± 6.0	22.2 ± 4.4	0.7805
Airway 3	23.3 ± 5.3	23.9 ± 4.0	0.6792
Airway 4	7.9 ± 3.5	7.0 ± 3.3	0.4895
Airway 5	8.2 ± 2.0	8.5 ± 2.6	0.7581
Airway 6	10.4 ± 5.7	10.4 ± 3.8	0.9631
Airway 7	17.7 ± 3.0	18.6 ± 4.8	0.6340

OSA patients vs. Population Means

There were statistically significant differences between OSA subjects and population means for 11 of the 22 cephalometric measurements (Table 7). OSA subjects showed an increased overjet, decreased cranial base angles, increased cranio-cervical angle, decreased mandibular incisor angulation, increased distance between the hyoid bone and the inferior border of the mandible, increased soft palate length, increased airway at Airway 1, and decreased airway at Airways 3, 4, and 5.

Table 7. Comparison of craniofacial structures of OSA patients and population mean

Variable	Mean	S.D.	95% C.I. Lower	95% C.I. higher	Pop Means
SNA	81.5	4.94	80.317	82.6917	82±3.5
SNB	78.8	4.79	77.69758	80.00097	80±3.0
ANB	2.68	2.90	1.985122	3.377197	3.0±2.5
OJ*	3.18	1.79	2.750404	3.609017	2.5±2.5
OB	2.13	1.94	1.663077	2.594894	2.5±2.0
NSAr*	121.4	5.78	120.002	122.7806	124±5.0
NSBa*	126.0	5.93	124.6245	127.4741	131±4.5
NSL/OPT*	109.4	7.84	107.5338	111.301	94.6±7.39
PP/SN	7.5	3.73	6.587051	8.381065	7.3±3.5
MP/SN	32.4	6.93	30.72081	34.0502	33±6
PP/MP	24.9	5.80	23.50914	26.29376	25±6
U1/PP	109.8	6.88	108.1752	111.4828	110±5.0
L1/MP*	93.1	6.85	91.40486	94.69659	95±7
MP-H*	22.5	5.77	21.04748	24.00498	15±2
PNS-P*	39.4	4.25	38.33603	40.37701	37.2 ± 4.7
Airway 1*	10.5	3.26	9.693465	11.26016	9.10±1.85
Airway 2	22.2	4.53	21.09806	23.27295	23.15±3.23
Airway 3*	23.9	4.13	22.88344	24.86728	25.69±2.90
Airway 4*	7.1	3.28	6.279467	7.853866	10.09±2.80
Airway 5*	8.5	2.52	7.847628	9.05672	11.79±2.77
Airway 6	10.4	3.95	9.488809	11.38655	9.30±3.06
Airway 7	18.5	4.61	17.37297	19.58645	18.59±2.27

Correlation Analysis of Lateral Cephalometric Measurements

Airway 4, the retropalatal airway, was positively correlated with maxillary incisor angulations (r = 0.4158). Airway 5 and 7 were positively correlated with AHI (r = 0.3554 and 0.3214, respectively). Airway 7 was also positively correlated with NSL/OPT, cranio-cervical angle (r = 0.3553). Soft palate length, PNS-P was negatively correlated with MP/SN, mandibular plane angle (r = -0.3195). MP-H, the distance between Hyoid bone to mandibular plane was positively correlated with Mandibular plane angle, MP/SN (r = 0.3174). MP-H was negatively correlated with Mandibular incisor angulations, L1/MP (r = -0.3848).

Table 8. Pearson Correlation Analysis Matrix (Cephalomeric Measurements)

	AHI	O_2 < 90%	BMI	SNA	SNB	ANB	OJ	OB	NS-Ar	NS-Ba	NSL/OPT
AHI	1.0000										
Below 90	-0.0671	1.0000									
BMI	0.2236	0.1421	1.0000								
SNA	-0.0644	-0.0206	-0.0787	1.0000							
SNB	-0.1033	-0.0391	-0.1038	0.8500	1.0000						
ANB	-0.0639	0.0292	0.0419	0.2105	-0.3326	1.0000					
OJ	0.0855	-0.0779	0.1285	-0.1161	-0.2415	0.2651	1.0000				
OB	-0.2082	-0.1316	0.0079	0.1444	0.1908	-0.0895	0.4232	1.0000			
NSAr	0.1910	0.0585	0.0702	-0.3347	-0.3852	0.1318	0.3306	0.0381	1.0000		
NSBa	0.1618	-0.0588	0.0980	-0.3664	-0.4276	0.1455	0.2790	0.0623	0.9057	1.0000	
NSL/OPT	0.2673	-0.0531	0.2138	-0.3689	-0.5609	0.3641	0.0756	-0.3050	0.0696	0.0909	1.0000
PP/SN	-0.0069	-0.0128	0.0262	-0.2017	-0.4430	0.4610	-0.0631	-0.2560	0.0917	0.0859	0.3543
MP/SN	0.0849	0.0769	0.1690	-0.4341	-0.6556	0.4461	-0.0610	-0.3566	0.2023	0.2831	0.5272
PP/MP	0.1003	0.0972	0.1798	-0.3813	-0.4960	0.2453	-0.0360	-0.2614	0.1791	0.2761	0.4018
U1/PP	0.0934	0.0185	-0.0365	0.4707	0.5182	-0.1117	-0.0472	-0.1482	-0.0232	-0.1223	-0.1815
L1/MP	0.0976	0.1425	-0.0634	0.0617	-0.1701	0.4220	0.0378	-0.1924	0.1244	0.0877	0.0936
AW 1	-0.1547	-0.1644	-0.0970	-0.0271	0.0107	-0.0255	0.2757	0.1472	0.1608	0.1522	-0.0528
AW 2	-0.1581	0.0254	-0.0490	-0.0381	0.0410	-0.1203	0.2406	0.1800	0.0953	0.0155	0.0398
AW 3	0.0178	0.0252	0.0105	-0.2024	-0.1768	-0.0105	0.2384	0.0567	0.1761	0.1784	0.2131
AW 4	0.2322	-0.0652	-0.0446	0.1600	0.2658	-0.2279	-0.1902	-0.2383	0.1175	0.0911	0.0587
AW 5	0.3554	-0.3553	0.1267	0.2402	0.2014	0.0191	-0.0586	-0.1845	-0.0049	0.0904	0.1705
AW 6	0.2111	0.0415	0.2497	0.1609	0.1848	-0.0564	0.0722	0.0811	-0.1208	-0.1193	0.1238
AW 7	0.3214	-0.2241	0.1119	-0.0661	-0.0414	-0.0501	0.1677	0.0934	0.3621	0.3158	0.3553
PNS-P	0.0173	-0.0675	-0.0619	0.0696	0.0687	-0.0085	-0.0082	-0.0532	-0.0549	-0.0780	-0.0870
MP-H	0.0624	0.0977	0.1182	-0.1178	-0.1654	0.0744	-0.0955	-0.0989	-0.1092	-0.0781	0.2315

Table 8. (Continued)

	PP/SN	MP/SN	PP/MP	U1/PP	L1/MP	AW 1	AW 2	AW 3	AW 4	AW 5	AW 6
PP/SN	1.0000										
MP/SN	0.4987	1.0000									
PP/MP	-0.0093	0.8621	1.0000								
U1/PP	-0.0383	-0.1401	-0.1387	1.0000							
L1/MP	0.1431	-0.1052	-0.2047	0.1655	1.0000						
AW 1	-0.1670	-0.0781	0.0070	-0.1286	-0.1912	1.0000					
AW 2	-0.2015	-0.1608	-0.0674	-0.1327	-0.2036	0.4792	1.0000				
AW 3	-0.0772	-0.0230	0.0185	-0.2496	-0.0202	0.4669	0.7298	1.0000			
AW 4	-0.0948	-0.2596	-0.2433	0.4158	0.1064	-0.0064	0.0980	0.1378	1.0000		
AW 5	-0.0984	-0.1059	-0.0638	0.3419	0.0435	-0.0605	-0.0011	0.1251	0.6375	1.0000	
AW 6	-0.0289	-0.2158	-0.2323	0.0243	-0.0583	-0.0941	0.2115	0.2096	0.2606	0.4251	1.0000
AW 7	-0.0375	0.0213	0.0479	0.0333	-0.1566	0.2619	0.1758	0.1188	0.1828	0.2289	0.1470
PNS-P	0.0541	-0.2498	-0.3195	-0.1697	0.2506	-0.0878	0.0432	0.2322	-0.1871	-0.0752	0.1504
MP-H	0.1416	0.3174	0.2832	-0.1712	-0.3848	-0.0948	0.0015	-0.0588	-0.0296	0.1598	-0.0167
	AW 7	**PNS-P**	**MP-H**								
AW 7	1.0000										
PNS-P	-0.0209	1.0000									
MP-H	0.1328	-0.0848	1.0000								

Correlation: Cephalometric Variables vs. DISE

Location of obstruction

We compared each cephalometric variable between subjects who had obstruction at palate level (n=66) and subjects who did not (n=3) (Table 9). Maxillary incisor angulations (U1/PP) was reduced in subjects who had obstruction at palate level compared to subject who did not.

There were 62 subjects who had obstruction at the hypopharynx level and 7 subjects who did not. Airway 5, airway dimension at the uvula level, was reduced in subjects who had obstruction at hypopharynx level compared to subjects who did not (Table 10).

Correlation: Cephalometric Variables vs. DISE

Severity of obstruction

The mean overbite of the subjects with a moderate (50 to 75%) degree of obstruction at palate level was 0.15 ± 2.0 mm compared to 2.2 ± 1.8 mm for subjects with severe (>75%) obstruction ($p < 0.01$) (Table 11). There was no correlation between cephalometric variables and DISE results in regards to the severity of obstruction at the hypopharynx level (Table 12).

Table 9. Cephalometric Measurements and Presence/Absence of Palatal Obstruction

	Obstructed at palate? Yes (n=66)	Obstructed at palate? No (n=3)	P value
SNA	81.6 ± 4.8	79.2 ± 8.5	0.4130
SNB	79.0 ± 4.8	75.7 ± 4.5	0.2476
ANB	2.64 ± 2.8	3.5 ± 4.8	0.6203
PNS-P	39.5 ± 4.2	36.2 ± 3.4	0.1903
MP-H	22.5 ± 5.9	23.4 ± 2.1	0.7828
OJ	3.2 ± 1.8	3.0 ± 0.8	0.8602
OB	2.0 ± 1.9	4.1 ± 1.8	0.0767
NSAr	121.3 ± 5.8	124.3 ± 4.2	0.3715
NSBa	126.0 ± 6.0	128.5 ± 4.2	0.4684
NSL/OPT	109.5 ± 7.9	107.7 ± 7.8	0.7011
PP/SN	7.5 ± 3.8	6.5 ± 3.5	0.6554
MP/SN	32.4 ± 6.9	31.6 ± 9.3	0.8426
PP/MP	24.9 ± 5.7	25.1 ± 9.8	0.9602
U1/PP	110.5 ± 6.1	95.5 ± 9.6	0.0001*
L1/MP	93.0 ± 6.7	94.9 ± 10.8	0.6361
Airway 1	10.5 ± 3.3	9.6 ± 2.3	0.6374
Airway 2	22.2 ± 4.4	21.2 ± 7.9	0.7028
Airway 3	24.0 ± 4.1	21.1 ± 5.6	0.2367
Airway 4	7.1 ± 3.3	6.8 ± 2.7	0.8867
Airway 5	8.5 ± 2.5	8.3 ± 2.3	0.8973
Airway 6	10.4 ± 3.9	11.1 ± 5.9	0.7577
Airway 7	18.4 ± 4.7	19.7 ± 2.6	0.6244

Table 10. Cephalometric Measurements and Presence/Absence of Hypopharynx Obstruction

	Obstructed at hypopharynx? Yes (n=62)	Obstructed at hypopharynx? No (n=7)	P value
SNA	81.6 ± 5.0	81.2 ± 4.8	0.8335
SNB	78.8 ± 4.7	79.0 ± 5.8	0.8969
ANB	2.8 ± 2.9	2.1 ± 3.1	0.5469
PNS-P	39.7 ± 4.3	37.1 ± 3.3	0.0891
MP-H	22.5 ± 5.8	22.8 ± 6.3	0.9024
OJ	3.1 ± 1.5	3.5 ± 3.1	0.5953
OB	2.0 ± 2.0	3.2 ± 1.3	0.0724
NSAr	121.5 ± 5.9	120.1 ± 5.5	0.7822
NSBa	126.1 ± 6.1	125.6 ± 4.7	0.8003
NSL/OPT	109.0 ± 7.7	112.3 ± 8.4	0.2343
PP/SN	7.7 ± 3.8	6.2 ± 2.7	0.2594
MP/SN	32.9 ± 7.2	29.5 ± 3.7	0.1858
PP/MP	25.1 ± 6.1	23.4 ± 3.4	0.3948
U1/PP	110.2 ± 6.9	107.5 ± 6.6	0.2867
L1/MP	93.4 ± 6.3	91.0 ± 9.8	0.3367
Airway 1	10.5 ± 3.3	10.4 ± 3.4	0.9058
Airway 2	22.2 ± 4.7	21.8 ± 3.2	0.7924
Airway 3	23.9 ± 4.4	24.0 ± 2.3	0.9780
Airway 4	7.1 ± 3.4	7.0 ± 2.0	0.9570
Airway 5	8.2 ± 2.6	10.0 ± 1.2	0.0454*
Airway 6	10.2 ± 4.1	12.2 ± 2.2	0.1474
Airway 7	18.1 ± 4.6	21.1 ± 4.1	0.0705

Table 11. Cephalometric Measurements and the Severity of Palatal Obstruction

	50 to 75% obstruction at palate level (n=6)	More than 75% obstruction at palate level (n=60)	p- value
SNA	83.1 ± 4.4	81.5 ± 4.8	0.4192
SNB	79.5 ± 3.7	78.9 ± 4.9	0.7742
ANB	3.6 ± 1.7	2.6 ± 2.9	0.3988
PNS-P	42.3 ± 2.7	39.2 ± 4.3	0.0965
MP-H	21.2 ± 4.4	22.6 ± 6.1	0.5749
OJ	2.5 ± 2.3	3.3 ± 1.8	0.3019
OB	0.2 ± 2.0	2.2 ± 1.8	0.0100*
NSAr	122.3 ± 7.3	121.2 ± 5.7	0.6394
NSBa	124.9 ± 7.4	126.0 ± 5.9	0.6602
NSL/OPT	108.7 ± 7.5	109.6 ± 8.0	0.7897
PP/SN	9.2 ± 3.4	7.4 ± 3.8	0.2519
MP/SN	33.5 ± 5.3	32.3 ± 7.1	0.6640
PP/MP	24.4 ± 6.0	24.9 ± 5.7	0.8308
U1/PP	113.1 ± 5.1	110.2 ± 6.1	0.2676
L1/MP	94.9 ± 3.4	92.8 ± 7.0	0.4573
Airway 1	8.6 ± 1.4	10.7 ± 3.4	0.1306
Airway 2	21.4 ± 3.9	22.3 ± 4.5	0.6255
Airway 3	24.3 ± 2.8	24.0 ± 4.2	0.8520
Airway 4	7.3 ± 3.1	7.1 ± 3.4	0.8756
Airway 5	8.8 ± 2.4	8.4 ± 2.6	0.7220
Airway 6	9.7 ± 4.4	10.5 ± 3.9	0.6455
Airway 7	16.3 ± 4.9	18.6 ± 4.6	0.2437

Table 12. Cephalometric Measurements and the Severity of Hypopharynx Obstruction

	50 to 75% obstruction at hypopharynx (n=19)	More than 75% obstruction at hypopharynx (n=42)	p- value
SNA	81.6 ± 5.5	82.0 ± 4.8	0.7669
SNB	79.0 ± 5.4	79.3 ± 4.3	0.8380
ANB	2.6 ± 3.1	2.8 ± 2.9	0.8165
PNS-P	39.4 ± 5.3	39.7 ± 3.9	0.7713
MP-H	22.8 ± 5.4	22.0 ± 5.6	0.6302
OJ	2.5 ± 1.9	3.2 ± 1.6	0.1483
OB	2.2 ± 1.4	1.9 ± 2.1	0.9381
NSAr	122.3 ± 6.1	120.6 ± 6.0	0.3335
NSBa	127.4 ± 5.5	125.2 ± 6.3	0.1908
NSL/OPT	107.9 ± 6.3	109.6 ± 8.5	0.4609
PP/SN	7.7 ± 4.0	7.6 ± 3.8	0.8694
MP/SN	33.0 ± 6.6	32.4 ± 7.0	0.7605
PP/MP	25.3 ± 5.2	24.8 ± 6.2	0.7593
U1/PP	110.6 ± 6.9	110.3 ± 6.9	0.5578
L1/MP	93.3 ± 6.7	93.2 ± 6.3	0.9804
Airway 1	9.5 ± 3.3	10.9 ± 3.4	0.1326
Airway 2	22.0 ± 5.1	22.3 ± 4.5	0.8026
Airway 3	23.3 ± 3.8	24.3 ± 4.4	0.4124
Airway 4	7.8 ± 4.6	6.9 ± 2.8	0.3638
Airway 5	8.4 ± 3.1	8.3 ± 2.4	0.8497
Airway 6	9.8 ± 4.0	10.6 ± 4.2	0.4711
Airway 7	16.6 ± 4.4	19.0 ± 4.8	0.0735

Correlation: Cephalometric Variables vs. DISE

Obstructing Structures at Palate level

The palate, tonsils, and lateral pharyngeal walls were considered as the anatomical structures that could potentially contribute to obstruction at the palate level. The palate was the principal obstructing structure for 33 subjects as defined by the DISE evaluation. Tonsils were found to be the principal obstructing structure for 27 subjects, and for the remaining 9 subjects it was found to be lateral pharyngeal walls.

We found four cephalometric variables that were statistically different between palate and tonsil groups at $p < 0.05$; MP-H, overjet, Airway 2 and L1/MP. MP-H was significantly longer in the palate group compared to the tonsil group. Overjet for the palate group was 3.6 ± 1.7mm, whereas the same variable for the tonsil group was 2.7 ± 1.9mm. Airway 2 for the palate group was 23.4 ± 4.3mm, whereas it was 21.2 ± 4.6mm for the tonsil group. Mandibular incisor angulation was more upright in the palate group than the tonsil group. The findings of this t- test are listed in Table 13.

Table 14 shows the results of t- test between the palate group and the lateral pharyngeal wall group. Airway 4 and PP/SN were statistically different between the two groups at $p < 0.05$. Palate group showed significantly reduced airway 4 measurement than the lateral pharyngeal wall group. PP/SN was increased in the lateral pharyngeal wall group than the palate group.

MP-H and PP/SN were two variables that were statistically different between the tonsil and the lateral pharyngeal wall groups at $p < 0.05$ (Table 15). MP-H was greatly increased in lateral pharyngeal wall group compared to the tonsil group. PP/SN was increased in the lateral pharyngeal wall group compared to the tonsil group.

Correlation: Cephalometric Variables vs. DISE

Obstructing Structures at Hypopharynx level

Three anatomical structures were considered as located at the hypopharynx level: the tongue, epiglottis, and lateral pharyngeal walls.

The three variables were statistically different between the tongue and epiglottis groups at $p < 0.05$ (Table 16): overjet, overbite, and PP/SN (palatal plate angle). Overjet was increased in the epiglottis group compared to the tongue group. Overbite in the tongue group was 1.6 ± 2.1mm, whereas it was 3.0 ± 1.3mm in the epiglottis group. Finally PP/SN in the tongue group was 8.1 ± 3.3°, whereas it was 4.4 ± 3.6° in the epiglottis group.

One variable was significantly different between the tongue group and the lateral pharyngeal wall group at $p < 0.05$ (Table 17). PP/MP in the tongue group was 26.0 ± 5.9°, whereas it was 21.5 ± 6.3° in the lateral pharyngeal wall group.

Two variables were significantly different between the epiglottis group and the lateral pharyngeal wall group at $p < 0.05$ (Table 18). Overjet in the epiglottis group was 4.2 ± 1.8mm, whereas it was 2.6 ± 1.1mm in the lateral pharyngeal wall group. PP/SN in the epiglottis group was 4.4 ± 3.6°, whereas it was 10.1 ± 3.8° in the lateral pharyngeal wall group.

Table 13. Cephalometric Measurements and the primary structure for Palatal Obstruction palate *vs*. tonsils

	Obstructing structure Palate (n=33)	Obstructing structure Tonsil (n=27)	p- value
SNA	82.2 ± 5.2	81.4 ± 4.1	0.5133
SNB	79.5 ± 5.3	78.9 ± 4.1	0.6642
ANB	2.8 ± 3.3	2.5 ± 2.3	0.6776
PNS-P	39.8 ± 4.5	38.9 ± 4.0	0.4140
MP-H	24.2 ± 5.8	20.0 ± 5.8	0.0054*
OJ	3.6 ± 1.7	2.7 ± 1.9	0.0539*
OB	2.2 ± 1.9	1.9 ± 2.0	0.6373
NSAr	120.5 ± 5.6	122.0 ± 5.7	0.3285
NSBa	125.1 ± 6.6	126.8 ± 4.9	0.2696
NSL/OPT	108.4 ± 9.1	110.1 ± 6.4	0.3994
PP/SN	7.5 ± 4.0	6.7 ± 2.9	0.4507
MP/SN	32.9 ± 6.8	31.1 ± 6.8	0.3122
PP/MP	25.5 ± 5.4	24.4 ± 5.8	0.4600
U1/PP	110.5 ± 5.7	110.1 ± 6.6	0.7891
L1/MP	91.3 ± 7.3	95.2 ± 6.0	0.0321*
Airway 1	11.2 ± 3.4	10.2 ± 3.3	0.2743
Airway 2	23.4 ± 4.3	21.2 ± 4.6	0.0553*
Airway 3	24.5 ± 4.9	23.7 ± 3.0	0.5018
Airway 4	6.4 ± 3.3	7.3 ± 2.7	0.2256
Airway 5	7.8 ± 2.4	9.0 ± 2.6	0.0930
Airway 6	10.0 ± 3.8	10.8 ± 3.4	0.4421
Airway 7	18.0 ± 4.7	19.2 ± 4.2	0.2824

Table 14. Cephalometric Measurements and the primary structure for Palatal Obstruction palate *vs.* lateral pharyngeal walls

	Obstructing structure Palate (n=33)	Obstructing structure Lat.Pha.Wall (n=6)	p- value
SNA	82.2 ± 5.3	79.3 ± 5.2	0.2241
SNB	79.5 ± 5.3	76.7 ± 5.3	0.2507
ANB	2.8 ± 3.3	2.6 ± 2.7	0.9046
PNS-P	39.8 ± 4.5	40.7 ± 4.1	0.6675
MP-H	24.2 ± 5.8	26.0 ± 7.7	0.5122
OJ	3.6 ± 1.7	3.0 ± 1.6	0.4266
OB	2.2 ± 1.9	1.8 ± 2.2	0.6502
NSAr	120.5 ± 5.6	122.2 ± 8.0	0.5397
NSBa	125.1 ± 6.6	127.0 ± 7.1	0.5258
NSL/OPT	108.4 ± 9.1	113.0 ± 6.2	0.2437
PP/SN	7.5 ± 4.0	11.5 ± 3.8	0.0296*
MP/SN	32.9 ± 6.8	35.4 ± 7.7	0.4192
PP/MP	25.5 ± 5.4	24.0 ± 7.4	0.5551
U1/PP	110.5 ± 5.7	112.1 ± 6.2	0.5375
L1/MP	91.3 ± 7.3	92.3 ± 3.9	0.7620
Airway 1	11.2 ± 3.5	8.5 ± 1.4	0.0755
Airway 2	23.4 ± 4.3	20.7 ± 3.3	0.1465
Airway 3	24.5 ± 4.9	22.6 ± 3.5	0.3713
Airway 4	6.4 ± 3.3	9.8 ± 4.8	0.0335*
Airway 5	7.8 ± 2.4	9.6 ± 2.2	0.1128
Airway 6	10.0 ± 3.8	10.9 ± 6.5	0.6471
Airway 7	18.0 ± 4.7	17.4 ± 6.7	0.7924

Table 15. Cephalometric Measurements and the primary structure for Palatal Obstruction tonsils *vs.* lateral pharyngeal walls

	Obstructing structure Tonsil (n=27)	Obstructing structure Lat.Pha.Wall (n=6)	p- value
SNA	81.4 ± 4.1	79.3 ± 5.2	0.3005
SNB	78.9 ± 4.1	76.7 ± 5.3	0.2660
ANB	2.5 ± 2.3	2.6 ± 2.7	0.8960
PNS-P	38.9 ± 4.0	40.1 ± 4.1	0.3401
MP-H	20.0 ± 4.6	26.0 ± 7.7	0.0161*
OJ	2.7 ± 1.9	3.0 ± 1.6	0.7082
OB	1.9 ± 2.0	1.8 ± 2.2	0.8656
NSAr	122.0 ± 5.7	122.2 ± 8.0	0.9416
NSBa	126.8 ± 4.9	127.0 ± 7.1	0.9379
NSL/OPT	110.1 ± 6.4	113.0 ± 6.2	0.3246
PP/SN	6.7 ± 2.9	11.5 ± 3.8	0.0021*
MP/SN	31.1 ± 6.8	35.4 ± 7.7	0.1823
PP/MP	24.4 ± 5.8	24.0 ± 7.4	0.8768
U1/PP	110.1 ± 6.6	112.1 ± 6.2	0.5020
L1/MP	95.2 ± 6.0	92.3 ± 3.9	0.2659
Airway 1	10.2 ± 3.3	8.5 ± 1.4	0.2351
Airway 2	21.2 ± 4.6	20.7 ± 3.3	0.8048
Airway 3	23.7 ± 3.0	22.6 ± 3.5	0.4116
Airway 4	7.3 ± 2.7	9.8 ± 4.8	0.0916
Airway 5	9.0 ± 2.6	9.6 ± 2.2	0.5949
Airway 6	10.8 ± 3.4	10.9 ± 6.5	0.9396
Airway 7	19.2 ± 4.2	17.4 ± 6.7	0.3883

Table 16. Cephalometric Measurements and the primary structure for Hypopharynx Obstruction tongue *vs.* epiglottis

	Tongue (n=40)	Epiglottis (n=12)	p- value
SNA	80.9 ± 4.7	83.1 ± 5.4	0.1767
SNB	78.5 ± 4.7	80.4 ± 4.8	0.2384
ANB	2.4 ± 3.0	2.9 ± 3.0	0.6086
PNS-P	39.5 ± 4.2	38.6 ± 4.1	0.5628
MP-H	22.1 ± 5.5	22.5 ± 4.3	0.8624
OJ	2.7 ± 1.7	4.2 ± 1.8	0.0110*
OB	1.6 ± 2.1	3.0 ± 1.3	0.0347*
NSAr	121.6 ± 6.2	121.0 ± 6.2	0.7827
NSBa	126.8 ± 6.1	123.6 ± 6.3	0.1172
NSL/OPT	108.8 ± 7.8	107.7 ± 8.5	0.6928
PP/SN	8.1 ± 3.3	4.4 ± 3.6	0.0014*
MP/SN	34.0 ± 6.8	30.0 ± 7.7	0.0885
PP/MP	26.0 ± 5.9	25.6 ± 5.4	0.8704
U1/PP	110.6 ± 6.9	109.1 ± 7.6	0.5029
L1/MP	92.8 ± 6.7	93.5 ± 6.4	0.7316
Airway 1	10.3 ± 3.5	11.3 ± 3.2	0.3733
Airway 2	21.9 ± 4.7	24.1 ± 4.4	0.1468
Airway 3	23.6 ± 4.5	25.5 ± 3.3	0.1769
Airway 4	7.2 ± 3.3	6.7 ± 2.5	0.6065
Airway 5	8.0 ± 2.6	8.5 ± 2.6	0.5478
Airway 6	9.6 ± 3.6	11.7 ± 4.0	0.0879
Airway 7	17.7 ± 4.5	19.4 ± 3.8	0.2324

Table 17. Cephalometric Measurements and the primary structure for Hypopharynx Obstruction tongue vs. lateral pharyngeal walls

	Tongue (n=40)	Lat.Pha.Wall (n=10)	p- value
SNA	80.9 ± 4.7	83.5 ± 5.7	0.1419
SNB	78.5 ± 4.7	79.5 ± 5.4	0.5692
ANB	2.4 ± 3.0	4.0 ± 2.4	0.1164
PNS-P	39.5 ± 4.2	40.8 ± 5.2	0.3999
MP-H	22.1 ± 5.5	23.8 ± 7.4	0.4484
OJ	2.7 ± 1.7	2.6 ± 1.1	0.8363
OB	1.6 ± 2.1	2.1 ± 1.8	0.4829
NSAr	121.6 ± 6.2	120.2 ± 6.3	0.5446
NSBa	126.8 ± 6.1	125.2 ± 5.8	0.4531
NSL/OPT	108.8 ± 7.8	113.0 ± 7.6	0.1354
PP/SN	8.1 ± 3.3	10.1 ± 3.8	0.0919
MP/SN	34.0 ± 6.8	31.7 ± 7.0	0.3315
PP/MP	26.0 ± 5.9	21.5 ± 6.3	0.0403*
U1/PP	110.6 ± 6.9	110.3 ± 6.2	0.8847
L1/MP	92.8 ± 6.7	94.0 ± 5.4	0.6047
Airway 1	10.3 ± 3.5	10.4 ± 3.5	0.9327
Airway 2	21.9 ± 4.7	21.1 ± 4.6	0.6358
Airway 3	23.6 ± 4.5	22.7 ± 4.4	0.5572
Airway 4	7.2 ± 3.3	7.6 ± 4.8	0.7681
Airway 5	8.0 ± 2.6	9.3 ± 2.8	0.1838
Airway 6	9.6 ± 3.6	11.6 ± 5.7	0.1755
Airway 7	17.7 ± 4.5	19.1 ± 6.5	0.4127

Table 18. Cephalometric Measurements and the primary structure for Hypopharynx Obstruction epiglottis *vs.* lateral pharyngeal walls

	Epiglottis (n=12)	Lat.Pha.Wall (n=10)	p- value
SNA	83.1 ± 5.4	83.5 ± 5.7	0.8715
SNB	80.4 ± 4.8	79.5 ± 5.4	0.6933
ANB	2.9 ± 3.0	4.0 ± 2.4	0.3473
PNS-P	38.6 ± 4.1	40.8 ± 5.2	0.2913
MP-H	22.5 ± 4.3	23.8 ± 7.4	0.6354
OJ	4.2 ± 1.8	2.6 ± 1.1	0.0232*
OB	3.0 ± 1.3	2.1 ± 1.8	0.2065
NSAr	121.0 ± 6.2	120.2 ± 6.3	0.7468
NSBa	123.6 ± 6.3	125.2 ± 5.8	0.5449
NSL/OPT	107.7 ± 8.5	113.0 ± 7.6	0.1481
PP/SN	4.4 ± 3.6	10.1 ± 3.8	0.0016*
MP/SN	30.0 ± 7.7	31.7 ± 7.0	0.6099
PP/MP	25.6 ± 5.4	21.5 ± 6.3	0.1114
U1/PP	109.1 ± 7.6	110.3 ± 6.2	0.6910
L1/MP	93.5 ± 6.4	94.0 ± 5.4	0.8656
Airway 1	11.3 ± 3.2	10.4 ± 3.5	0.5314
Airway 2	24.1 ± 4.4	21.1 ± 4.6	0.1305
Airway 3	25.5 ± 3.3	22.7 ± 4.4	0.0965
Airway 4	6.7 ± 2.5	7.6 ± 4.8	0.5684
Airway 5	8.5 ± 2.6	9.3 ± 2.8	0.5310
Airway 6	11.7 ± 4.0	11.6 ± 5.7	0.9500
Airway 7	19.4 ± 3.8	19.1 ± 6.5	0.8962

DISCUSSION

Correlation between Cephalometry and DISE

This is the first study, to our knowledge, correlating the data from Lateral Cephalometry and DISE. It is significant since it may bridge the gap between the static and 2-dimensional imaging of lateral cephalometry a dynamic, 3-dimensional imaging of DISE. It is of great interests for many orthodontists who use traditional lateral cephalometry as their routine imaging system for orthodontic diagnosis and treatment planning.

Cephalometric Measurements vs. Presence of Obstruction

Through the Drug-Induced-Sleep-Endoscopy, OSA subjects were divided into subgroups: Obstruction group and non-obstruction group at either palate or hypopharynx level.

There were 66 subjects who had obstruction at the palate level, where there were 3 who did not have obstruction at the palate level. The obstruction group at palate level had maxillary incisors that were more upright compared to non-obstruction group at palate level ($95.5 \pm 9.6°$ vs. $110.5 \pm 6.1°$ at $p < 0.0001$). It is possible that the subjects who had obstruction at the palate level tend to position their tongue lower so they can increase their airway. Without the tongue being behind the maxillary incisors, counteracting the force from the lip, maxillary incisors might further retrocline. However, the sample size of the non-obstruction group was too small (n=3) to have enough power for the analysis.

In the hypopharynx analysis, Airway 5, airway at the uvula level, of the obstruction group was decreased compared to non-obstruction group (Table 10). Airway 6, the retrolingual airway, was also reduced in the obstruction group at the hypopharynx level, but this was not statistically significant at $p < 0.05$. Airway 7, airway dimension at epiglottis level, was also reduced in the obstruction group, and the p value of this finding was 0.0705.

Cephalometric Measurements vs. Primary structure for Obstruction

The palate group had a significantly increased value of MP-H, and more upright mandibular incisor angulation compared to the tonsil group (Table 13). Compared to the lateral pharyngeal wall group, the palate group had significantly reduced Airway 4 dimension.

Subjects whose OSA at the palate level was due to the palate seem to have characteristic anatomical structures on lateral cephalogram: reduced airway dimension at palate level, more upright mandibular incisor angulation, and more inferiorly positioned hyoid bone. It is interesting to note that they did not differ from either of the other groups in regards to the soft palate length. It seems as though the thickness of the palate, rather than the length of the palate is more important contributing to this pathology of obstructive sleep apnea.

OSA patients vs. Population Means

Commonly cited craniofacial structures that have been known to be associated with OSA include reduced SNA, SNB, longer and thicker soft palate, longer and thinker tongue, reduced AP dimension of pharynx, more inferiorly positioned hyoid bone relative to inferior mandibular border.

From our study, OSA subjects displayed distinctive craniofacial structures, many of which agree with the above findings (Table 7). The hyoid bone was 7.5mm more inferiorly positioned in OSA subjects compared to population means. However, it is important to note that this value is known to increase with age.[70] Taking into account the fact that the subjects in this study are middle-aged, hyoid bone displacement could be due to age and OSA. Airway 4 (retropalatal airway) and Airway 5 were 3mm smaller in OSA subjects than population means. This confirms the numerous findings of other studies in the OSA literature.[71-73] NSL/OPT was increased from the population mean by as much as 15 degrees.

These set of characteristics help identify potential patients who might have undiagnosed OSA that might benefit greatly from a proper referral for a further evaluation by an otolaryngologist.

Correlation Analysis of Lateral Cephalometric Measurements

Using Pearson correlation analysis, I attempted to find out if there were any skeletal and/or dentoalveolar variables that correlated with soft tissue measurements, *i.e.* Airway 1 through 7, soft palate length, and hyoid bone position.

Airway 5 and 7 were positively correlated with AHI (Table 8). Airway 7 was also positively correlated with NSL/OPT, the cranio-cervical angle. Airway 5 is decreased in the OSA subjects (Table 7). The OSA subjects seem to posture their head back by increasing the cranio-cervical angle to compensate for their constricted airway.

Limitations of the Study

This study was performed without control subjects not to expose healthy individuals to radiation or time-consuming and expensive DISE. There were good population norms data that we could utilize for the study, negating the need for our own control.

Although all the experimental lateral cephalograms were taken using a standardized setting of the cephalostat, there might be a minor discrepancy due to the use of different cephalostat machines.

Almost all the subjects had obstruction either at palate level (66 *vs.* 3) or hypopharynx level (62 *vs*. 7), making the comparison limited due to the small sample size of the non-obstruction group.

Future

It would be interesting to see the correlation between DISE findings and surgical treatment planning and/or outcome, since accurate diagnosis of the site of obstruction dictates the surgical treatment planning and outcome.

As the field of orthodontics has widened its horizon to 3-dimensional imaging, it should strive to come up with the norm value not only for skeletal and dentoalveolar measurements but also for airway area and volume.

CONCLUSIONS

This prospective cross-sectional study of 69 OSA subjects compared analyses using conventional lateral cephalometry and drug-induced-sleep-endoscopy (DISE). The following were found from the study:

1. OSA subjects had distinctive craniofacial structures that are different from population norms, and they include:
    a. Increased NSL/OPT
    b. Increased MP-H
    c. Decreased Airway 4, and 5
2. Lateral cephalometric variables that are shown to be correlated with soft tissue measurements include:
    a. Airway 5 and 7 were positively correlated with AHI
    b. Airway 7 was positively correlated with NSL/OPT
3. There were no correlations between lateral cephalometric variables and DISE severity findings.
4. DISE and lateral cephalometric analyses correlated well in regards to the location of airway obstruction in the following:
    a. Palate obstructers had more retroclined maxillary incisor angulation, and reduced Airway 4
    b. Hypopharynx obstructers had reduced Airway 5
5. DISE and lateral cephalometric analyses correlated well in regards to obstructing structures at the palate level in the following:

a. Subjects whose obstruction at the palate level was due to the palate, and not the tonsils, showed more upright mandibular incisor angulation and a more inferiorly positioned hyoid bone.
b. Subjects whose obstruction at palate level was due to palate, not lateral pharyngeal walls showed more decreased Airway 4.

Although two-dimensional and static, a cephalogram taken at a routine orthodontic examination could help a clinician to properly guide a patient who might have undiagnosed OSA that needs to be further evaluated by an otolaryngologist.

With the appropriate health history questionnaire, proper imaging and awareness of the clinician, our patients could benefit greatly from a routine orthodontic examination.

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