This paper is an epub ahead of print and has not yet been copyedited.

A Novel Method for Pre-selectivity of Oral Appliance Palliative Pharyngeal Airway Outcomes in Obstructive Sleep Apnea: A Pilot Study

Running Title: ***Who may increase airway dimensions with Oral Appliances for OSA?***

Bruce S. Haskell [a,b], David Jensen [c], Andrew M. Roberts [b], Mohamed Bazina [a]
University of Kentucky Department of Orthodontics [a], University of Louisville Department of Physiology [b], University of Florida Department of Orthodontics [c]

Abstract

Objectives: A qualified clinical solution improves pre-selective probabilities as who *may successfully use an* Oral Appliance *(OA) for* Obstructive Sleep Apnea *(OSA) for upright-awake oro-pharyngeal airway axial cross-sectional improvement.* A discrete value method was constructed measuring morphologic typology CBCT elements for OA use.

Materials and Methods: Subjects (n=20) diagnosed with OSA, and prescribed OAs were randomly selected for upright wakefulness airway imagery based on limited availability of imaging with and without an OA placement. Cross-sectional axial airway areas were calculated and divided into "good" and "poor" responders (≥16% or <16% respectively) for airway change. An Oral Appliance Evaluation Index (OAEI), using discrete scoring methods based upon morphologic typology was constructed evaluating the effectiveness of OA usage for upright awake minimal axial airway dimension improvement, providing a predictive model for anatomic responder type.

Results: Using OAEI, "good" and "poor" responders for upright awake axial airway area increase was predicted at a 70% accuracy (p=.02) from derived 2-D CBCT cephalometric values without the inclusion of the middle pharyngeal muscle vector change and 75.5% (p=.05) when middle pharyngeal measures were included.

Conclusion: Discrete scoring using cephalometric measures and middle pharyngeal muscle vector length change predicted OA palliative pharyngeal airway change. A 75.5% predictability for upright awake OSA subjects achieving a minimal cross-sectional axial airway area increase greater than or equal to 16% using an OA device was found for a calculated 77.5% increase of airway flow.

Clinical Implications: Who may increase airway dimensions is an effort, money, and time saver.

Abstract words: 248

Text words: 3995

Key words: Oral Appliance (MAD), Obstructive Sleep Apnea, Oro-pharyngeal predictability, Four-Bar Analyses

Introduction

Examination of morphologic typologies and biomechanical factors presents a method improving reliability of Oral Appliance (OA) use by pre-selecting upright-awake "good" vs. "poor" responders to minimal axial airway area increase in Obstructive Sleep Apnea (OSA) subjects.

Obstructive Sleep Apnea (OSA) occurs when airflow is obstructed by anatomical structures during sleep. This decrease in oxygen to the lungs is associated with hypopnic disturbances as sudden interruptions to sleep. Common characteristics of OSA include male gender, neck size larger than 17 inches, obesity, aging with oro-pharyngeal flaccidity and snoring.-OSA outcomes include daytime fatigue, cardiovascular events, high blood pressure, myocardial infarction, and stroke. [1] Despite the severity of co-morbidities, less than half of all subjects with OSA are treated.[2] Treatment begins with a polysomnogram where waking events are divided by sleep hours to calculate an Apnea-Hypopnea Index (AHI). AHI scores greater than 5 and less than 15 are “mild”; a 15-30 score is considered “moderate” while a score greater than 30 is noted as “severe”. The standard of care is a Continuous Positive Airway Pressure (CPAP) or Bi-level device (BiPap). [3] Other treatments include surgical advancement of the jaw(s) allowing airway structures ~~to be~~ positioned anteriorly, increasing airway volume and alternatively, the stimulation of the hypoglossal nerve.[4] Palliative function of OA’s for OSA is for reducing apneic episodes through improvement in airway patency. Positioning the mandible forward and opening the airway is intended to *increase airway volume* and resolve possible constriction points.[5]

Limited data is available how Oral Appliances may interactively influence physiological variables. For example, the hypoglossal nerve enables control of the hyoglossus, intrinsic, genioglossus and styloglossus muscles. Advancing the tongue with an OA, these muscles help open the airway. Hyoid position with an OA is also altered, and together with the tongue and mandibular position, helps to regulate pharyngeal airway dimensions. Forward positioning the mandible with an OA can increase velopharyngeal and genioglossal tension, opening the pharynx an *unspecified* amount, while the genioglossus and geniohyoid musculature hold the tongue forward and anteriorly from the back of the pharynx preventing airway occlusion. Advancement with an Oral Appliance reportedly increases basal electromyographic activity of the genioglossus, activating the palatoglossus and palatopharyngeal muscles and lateral walls of the velopharynx with ~~an~~ increased vertical dimension. This indirectly affects lateral wall tissue tonus. Airway baroreceptor/pressure receptors maintain systemic blood pressure with changes in orientation.[6.]

Aging, BMI, neck size, hypoglossal nerve function, neuromuscular feedback, including lateral wall function are all physiologic multi-factorial elements associated with OSA. Demographic factors as younger age, female gender, lower BMI, smaller neck circumference, retracted maxilla and mandible, narrower airway, shorter soft palate, and lower OSA severity are phenotypic features of good responses to OA use. [5,6]

OAs are prescribed by physicians as recommended by the American Academy of Sleep Medicine to patients with AHI values below 30. **[5]**

Limited Usefulness of Oral Appliances

Prior studies show limited correlations between OAs and improved AHI responses with SD values of reportedly successful treatment often approaching or exceeding the mean. A scoping review indicated individual OA application unpredictability with wide variability of AHI, 61.81% ± 12.29 related to predisposing factors.**[5]** One study reported only 39% of all patients may respond clinically with an OA advancement.[6]

Studies report weak anatomical significance with only general trends identifying no universal tendencies related to OA response. Negative OA outcomes may include unpredictable airway shape and volume changes, minimal axial airway areas, vertical position changes of the narrowest airway constriction point, canted hyoid positions and angulations as well as limiting the extent of anterior mandibular positioning through mandibular autorotation. **[5-17]**

OA prescription measures appear inconsistent and often indeterminate for palliative OSA treatment. This lack of correlation may be based upon unknown or incorrect assumptions of airway anatomy and kinematic effects. [5,18,19] The authors showed that AHI / Sleep Disturbed Breathing related to a specific anatomy is inconclusive. [5] Measuring *individual* anatomical structures or employing jaw advancement alone to treat OSA instead of an interaction of associated components appears simplistic.[20,21]

A Typological Focus for Airway Predictability

This pilot presents an anatomic-typological approach to airway volume improvement for OSA diagnosed subjects as a partial answer to OA pre-selectivity. A correlative conclusion relating sleep studies to verify the increase in airway as *resolving* sleep disturbed breathing is not intended. Instead, selected craniofacial typologies reveal the potential for improvement in pharyngeal minimal axial airway in upright awake subjects by identifying anatomic and biophysical changes with an OA. It is intended as a qualified practical pre-selective anatomical assessment in the recognition of "good" from "poor" responders for improvement in airway components as *"who may successfully use an OA for an enhancement of upright awake minimal axial airway dimensions".*

Methods and Materials

Subjects treated for OSA at the University of Louisville (n=20) self-reporting a subjective improved sleep response to OSA therapy with an OA were randomly selected for Herbst-type Oa's from a very limited existing subject population based upon availability of CBCT imaging with and without OA's. Subjects obtained from dental radiology archives were blinded from demographic and other physiologic data. Pre- and post-treatment objective sleep PSG data (including AHI) were not available for the cohort of patients. No additional

OSA diagnosed sample populations available with and without an OA with CBCT imagery were discovered. For diagnosis and treatment two CBCTs (i-CAT, Norcross GA) were taken with the patient awake in an upright sitting position, one in maximum intercuspation and the second with a Herbst-style OA positioning the jaw 75% of maximum protrusion. As sleep imaging units are not employed in ordinary clinical practice, this retrospective study used available CBCT imagery employing a standard upright awake unit. Boundaries of each scan were full cranial volumes extending to below the hyoid, except for one subject with a scan located by the superior boundary at the Frankfort Horizontal Plane. Data collection was IRB approved by University of Florida College of Dentistry (IRB # 202.06).

Imaging and Measures

Scans were de-identified and imported as DICOM files into Dolphin 3D Imaging Software (version 11.95, Chatsworth, California) via secure server to the University of Louisville under project approval of IRB202002352, with AHI values blinded from examiners. The "Airway Analysis" tool within Dolphin Imaging was used to define the sagittal borders of the airway by a box with vertices at the posterior nasal spine, basion, the anterior inferior border of the C3 vertebrae and the central body of the hyoid. The area of interest was defined by a "seed" placed in the airway space toggled to ensure a smooth border of the lumen. The analysis tool calculated total volume and minimum axial airway areas for each subject (Figure 1). The difference in the length of the vector of the middle pharyngeal constrictor muscle was taken from both appliance and non-appliance CBCT scans. Vector length was measured from the pharyngeal tubercle to the greater horn of the hyoid. Tracings were completed using the “digitize” tool on all extracted cephalograms in maximum intercuspation by using the “Build X-ray” tool from each CBCT.

Three-dimensional superimpositions of each subject with and without the OA in place were performed with airway changes calculated from the difference in measures with and without appliances in place.

These measures are associated with mandible/airway position: *ANB,* (skeletal classification) *Wits,* (anteroposterior jaw position): the position of the maxilla and mandible relative to each other and their relation to the occlusal plane. *ODI* (Overbite Depth Indicator): the plane connecting A point from B point to the mandibular plane angle plus or minus the palatal plane to Frankfurt horizontal plane, and the middle pharyngeal constrictor muscle vector length.[5,22] (Appendix 1) Airway volume and upright awake minimal axial areas were measured; made from the calculated lateral cephalometric (2D) image from CBCT imaging.

A disadvantage of practitioner accessibility using “in office” CBCT’s is a necessity for upright awake posture during imaging instead of using a sleep functional CBCT/MRI. The authors believed an “average” airway measure with CBCT was perhaps a best compromise for assessment of axial volume. Hospital CT while supine is a source of high millisieverts and not available.

Dimensional Aspects of Airflow

The narrowest axial lumen follows Bernoulli’s principles of ~~a~~ narrowed aperture: increased velocity, more turbulence, and *reduced* volume of flow. The responders were divided into respective subgroups, expecting that the collected data would follow a standard distribution. To divide “good” from “poor” enhanced anatomic responders a threshold value of 1 standard deviation below the mean was selected. This threshold value of -1 standard deviation translated to an equal value of Standard Score which when applied to a negative value z-table yielding a value of 0.15866 or 15.866% which rounded to the nearest whole number is 16%. Thus, a 16% upright awake minimal axial airway increase was used as the division between “good” and “poor” enhanced anatomic responders. This is judged substantial as Poiseuille's laminar flow equation conveys exponential output of flow.[23] (Q = flow, P = pressure, r = tube radii, l = length of tube, n= viscosity of air.) If all variables of the equation are standardized between two events and the only variable to change was the radius, then given an event with a radius =1, the flow (Q) would be 0.4. If the radius is increased by 16% (r =1.16) the output of this model is Q = 0.71. This yields a 77.5 % increase of flow: a reasonable threshold for dividing responder types. The radius of the pharynx increases with advanced jaw position; the area from transverse and antero-posterior movements decreases airway resistance by a factor of the radius to the fourth power.[7,23]

$$Q = \frac{\pi \mathrm{P} r^4}{8\eta l}$$

Anatomically, “good responders” above 16% have substantially enhanced upright awake minimal axial dimensions, while “poor upright awake axial airway enlargement responders” to a minimal extent below a 16% threshold may also develop some improved airflow based on Poiseuille's laminar flow equation.

Airway volume and minimal axial areas were measured in all upright awake subjects. Intra-evaluator reliability evaluation was completed by a selection of three cephalometric variables measured twice, one month apart, on five different cephalometric radiographs.

The Kappa score was calculated (0.89) for reproducibility and consistency. Quantitative and qualitative observations were recorded with respect to modeling the highest values for both specificity and sensitivity.

Results

A change in cross-sectional airway area occurred with all 20 upright awake subjects in the pool for both good and poor responders. Overall, this represented an average improved axial airway area of 27% with an OA. Eleven individuals were identified with an increased upright awake minimal axial area greater than or equal to 16% ("good responders") and 9 individuals with an axial area less than 16% ("poor responders") (Table 1). The "good" responders presented an average 56.6% minimum upright awake axial airway area *improvement*, while the "poor" averaged a *decrease* of 2.5% upright awake axial airway area change.

The Oral Appliance Efficacy Index (OAEI)

The OAEI is a constructed *discrete variable* classification index of selected morphologic variables using weighted scores to predict the axial cross-section of the airway with an OA at the threshold of 16%. Data sets are considered discrete if the values belonging to the set are distinct and separate; similar methodology is applied in the Pediatric Sleep and "STOP-BANG" disturbed sleep questionnaires.[24,25] Reviews indicated that *continuous variables* of cephalometric data are limited for predicting airway.[5] Here, specific *typology* cephalometric value composite scores of discrete measures were developed to evaluate OA predictive improvement for upright awake minimal axial airway area change.

The OAEI allows prediction of good or poor upright awake minimal axial airway response based upon a numerical threshold. Table 2 shows the four variables that were considered: ANB, Wits, ODI, and the change of the length of the middle pharyngeal muscle vector when an OA is placed. If a subject met specific threshold values, they were given the corresponding point values: ANB >4, Wits > 3, ODI >70, middle pharyngeal muscle change >-3. The point values were ascribed based on the standard deviation of the normative values for each variable with the greater the SD corresponding to a larger assigned point value. OAEI weights were based on required measures with 2 of the scores selected as 1 SD from the norms. The *Wits* score required an OAEI of 3 SDs from the norm as a *Wits SD* is small. A Wits above 3 SD embodies mandibular retrusion. As there is no current mean value for the length of the middle pharyngeal muscle length, the median score was assigned as an OAEI point value. The sum of these values ranging from 0-8 becomes the calculated score. (Appendices 1,2 & 3)

To prevent self-confirmational bias of the data, a random selection of half of the subject pool was used to identify the proposed variables before the complete cohort would be tested against the extrapolated threshold values. All subjects (11 "good" and 9 "poor" anatomic responders) were assessed with the OAEI twice, once with ANB, Wits, ODI and the change of the middle pharyngeal muscle length after placement of an OA; and again, using only ANB, Wits, and ODI scores.

<u>OAEI *without inclusion* of the middle pharyngeal muscle vector length change</u> (Table 3): Threshold of response type was set with an OAEI score of ≥3. Of the 20 subjects evaluated, 8 of the 11 "good" responders (73%) met the expected outcome, while 6 out of 9 of the "poor" responders (67%) met their expected outcome. Pooling these data, the

overall predicted outcome for evaluating the efficacy of the OAEI on the test subjects in this data set was 70% with a p-value of 0.02.

OAEI *including vector length* of middle pharyngeal muscle change (with and without the OA) (Table 4): The threshold including the middle pharyngeal muscle vector length change was set at an OAEI score of ≥5. The OAEI value threshold was increased in this iteration of the index because of the inclusion of an additional variable (the middle pharyngeal muscle length change). When applied to the 20 subjects in this study there was no difference with the index not including the middle pharyngeal muscle as 8 of the 11 “good” responders met the expected outcome with an accuracy also equaling 73%. However, the accuracy increased to 78% when evaluating “poor” responders with 7 of 9 subjects meeting the expected lowered criteria. Together, the “good” and “poor” anatomic responders resulted in a predictive value of 75.5% (p-value = 0.05) calculated by the average of accuracy in both responder types being correctly identified.

$$\text{AVERAGE (good" responders + "poor" responders)} \quad = \quad \text{OAEI predictive value}$$

$$\left(\frac{73\% + 67\%}{2}\right) = \mathbf{70}\% \text{ OAEI predictive value } \boldsymbol{not} \text{ including middle pharyngeal muscle}$$

$$\left(\frac{73\% + 78\%}{2}\right) = \mathbf{75.5}\% \text{ OAEI predictive value including middle pharyngeal muscle}$$

Discussion

Stomatognathic System

While ideal for evaluating OSA subject airways, *supine* sleep functional CBCT/MRIs, are not typically available in an office setting. With practitioner accessible "in-office" upright CBCT imaging, an awake posture is lamentably requisite. Methodology using upright awake CBCT images for OSA subjects for improving the probabilities for OA efficacy is understood as qualified. It may be considered a practitioner based, improved method over *indeterminate* OA construction with limited effectiveness. Pre-selective enhanced methodology CBCT measures of OA usage for airway improvement may support or eventually circumvent multi-disciplinary invasive methods such as drug sleep-induced endoscopy (DISE) to determine if optimal jaw positioning is acceptable for OSA subjects.[26]

Idiosyncrasies of Mandibular Advancement for Airway Enhancement

Specific mechanisms for developing airway patency with OAs are not well understood. A conundrum exists in that all subjects subjectively self-reported "improvement in sleep", while the data indicates poor anatomic responders *did not* have an improvement in upright awake axial airway volume. A recent paper using Oral Appliances (MAD), measuring AHI improvement reports, partly clarifies this enigma with similar findings. *"At first follow-up after MAD delivery, non-responders (no AHI improvement) reported* <u>*less*</u> *tiredness upon awakening (p = 0.003), better sleep quality (p = 0.005), and greater subjective improvement (p = 0.012) than (*AHI improvement*) responders. Among significant OSA symptoms, tiredness upon awakening, poorer sleep quality, and less subjective improvement were consistently found as predictors of (*AHI improvement*)* *treatment response…. This incongruity further complicates the determination of an appropriate endpoint to MAD advancement by the qualified dentist as in routine clinical setting…"*[6]

Enigmatically, we also report upright awake poor anatomic responders as less than 16% axial airway enlargement, subjectively self-reporting sleep *improvement*. A small portion of the latter may have some degree of patency improvement due to mild airway improvement and unknown factors possibly indirectly affecting lateral wall tissue tonus.[6] Additionally, a placebo effect may exist known psychologically as "response bias" / "courtesy bias", or ~~as~~ placebo effect. With the former, an OA subject wishes to assist in the treatment process by telling the practitioner what he desires to hear. Ideally, all *subjective* subject responses should be properly verified by measurable data as with polysomnography.

Differences in mandibular motion and structure relate to unpredictable alterations of airway volume.[27] Appliances protruding the mandible often combine with confounding vertical anatomical and rotational effects. For example, hyper-divergent subjects with increased clockwise rotation of the mandible on wide opening can re-position soft and hard tissues, moving the tongue posteriorly and obstructing airway structures.[5] Compounding this effect, obtusely angled OA distention jigs and appliance thickness may produce unwanted vertical effects due to disocclusion before protrusion. Increasing vertical elements lead to mandibular posterior rotations causing a 0.3 mm reduction in the range of mandibular advancement for every 1 mm of vertical opening.[6] For subjects with a backward opening pattern of Posselt's envelope, an OA may be even less effective for OSA treatment.[5-13] Only 50 - 61% AHI reduction are typically gained using oral appliances for OSA.[5,19,20] *Application* of oral appliances are often indiscriminate, relying upon idiosyncratic aspects of *muscular tension* of pharyngeal musculature to improve airway instead of *"non-muscular" inflation* with a CPAP/BiPAP for patency.[5]

It is beyond the scope of this structural model to incorporate additional variables of neuromuscular, Central Nervous System, oro-pharyngeal flaccidity, obesity and aging issues. Instead, thirty-six different possible interactive anatomical aspects of OSA are suggested. Figure 2.[28]

Certain associations have previously been identified as balancing factors contributing to interconnectivity for patency including: airway lumen, EMGgg (genioglossus electromyogram), biomechanical influence and pharyngeal shape.[5] A relationship of AHI reduction with a specified minimal axial airway area with OA use is plausibly implied and recommends further study.

Classification of group typologies

Mandibular retrusion with a deficient oro-pharyngeal area is a known predictor for AHI reduction when using an OA. This typology includes vertical facial types including those with deficient ramal height, open bite tendency, and an inferiorly placed posterior nasal spine (PNS).[5,7,9,12] No current method is ideal due to multifactorial etiological inputs on the presentation of OSA. This is represented by the variance shown in Figure 3. If OAEI presented a perfect predictive measure, there would be two distinct peaks in this figure; however, employed as a qualified diagnostic tool, outliers are not unexpected. "Good" anatomic responder subjects with low OAEI scores considered outliers are explained by myriad factors not fitting the proposed model. For example, Class III prognathic subjects often display enlarged pharyngeal airways without mandibular retrusive characteristics and yet be good OA responders [29] (Figure 4). Specificity issues may include but are not limited to age, poor neuromuscular compensation (EMG), BMI, neck circumference, airway shape and hyoid position.

Four-Bar Biomechanical Analysis

Alteration of the middle pharyngeal constrictor is associated with changes in airway generating potential. This pharyngeal muscle allows the oro-pharynx to open efficiently with advancement of the mandible. EMG of muscle function requires invasive procedures while MRIs for 3D muscle origin and insertion were unavailable.

Instead, a four-bar analysis is used which consist of links which move relative to one another, measuring both displacement and angular change.[30] The four-bar graphic in Figure 5 is used to assess altered elements of change with angular jaw and hyoid movements limited to a 2D vector estimation of a complex 3D structure. The *middle pharyngeal* muscle (MPM) vector approximates both convoluted space and shape.

OA palliative alteration of the of the *middle pharyngeal* muscle (MPM) is related to reports that dilator muscle tone may alter airway.[31,32] This constrictor (yellow bar), can change vector angulation with appliance use, and may lengthen, shorten, or remain unaltered with OA placement. Jaw advancement with lengthening of this muscle may plausibly induce extra “play” or creep into the four-bar system. This suggests the middle pharyngeal musculature/hyoid link can function as a “slider-crank linkage” with a mild lengthening trend in those with less response to an OA. Including the muscle vector change increases the specificity of the OAEI from 70% to 75.5.

The discrete variable scoring was established with and without this measure using percentages of predictive reliability as not all clinicians have access to CBCT while others may prefer not to deliver additional radiologic exposure.

Clinical Worksheet

A worksheet (Appendix 1,2 and 3) is provided using cephalometric weighted variables (OAEI score ≥3) for clinicians to improve airway prediction percentages for subjects who may or may not profit from a palliative OA. Only one cephalometric image is required for predicted accuracy of 70%. If increase of predictive accuracy to 75.5% is desired, two CBCTs should be taken: one in centric relation and the second with a wax bite simulating an activated OA with three-fourths protrusion. The difference in the images of the middle pharyngeal muscle vector length from the pharyngeal tubercle to the hyoid is calculated for a complete score (OAEI ≥5) evaluation. The pharyngeal tubercle lies on the lower surface of the basilar portion of occipital bone and is the attachment of the pharyngeal raphe.

The raphe is the insertion for the pharyngeal constrictors including the middle pharyngeal constrictor. It originates from the greater and lesser cornu of the hyoid, inserting into the raphe. The yellow arrow represents a simple vector used for the length of this muscle in the OAEI supplementary analysis.[34] . To image the pharyngeal tubercle for the 4-bar analysis, a CBCT is suggested to facilitate the location of this structure. While it is possible to visualize an estimation of pharyngeal tubercle position with a lateral cephalometric image, scanning through a CBCT assures accuracy of imaging of the tubercle structure itself. Many practitioners now eschew the cephalometric X-ray machine and use a composite image of all dentition, cephalometric image, airway, adenoids and tonsils, etc. derived from CBCT alone. (Appendices, Figure 5).

Limitations of this study

Placing an OA device for simple mandibular advancement to ameliorate OSA without a planned outcome is an expensive invitation for limited effectiveness or outright failure.[33] The application of *composite biometric typology* in a limited pilot study of 20 upright-awake subjects for an *anatomical-specific* *CBCT analysis* without polysomnogram data (PSG), BMI, family history and other pertinent considerations is conceived as *preliminary* groundwork for future OSA studies. Incorporating muscular bio-engineering analysis, polysomnographic, demographic, and physiologic data, as well as validating subjective curative claims, is considered essential for improving predictive accuracy for successful application of OA devices. Prospective studies to validate a correlative key OAEI scoring for AHI reduction using demographics of age/gender/ BMI/ neck circumference/ ethnicity, etc. together with polysomnography and *sleep functional* CBCT / MRI are central. Larger data sets are required to resolve a) if the pilot constructed OAEI is validated for use as a reliable predictor of increased upright-awake minimal axial airway area with an OA, and b) if the upright-awake CBCT axial area airway percentage improvements for “good” anatomic responders’ match OA treated OSA subjects for improved PSG reduction scores.

Conclusion:

* The pilot OAEI model is a constructed, weighted index identifying typologies allowing a simplified quantification for pre-selective predictability of an OA for upright awake oro-pharyngeal airway enhancement.

* Using CBCT cephalometric measures, the model predicts upright awake airway enhancement for an OA in 70% of patients with mild to moderate OSA. Including the middle pharyngeal constrictor muscle with these data is proposed to predict upright awake airway enhancement of an OA in 75.5% of subjects.

* Good anatomic responder values existing at a threshold of greater than or equal to a 16% upright awake minimal axial airway area, yield an increased flow rate of more than 77.5%.

References:

1. Young T, Skatrud J, Peppard PE. Risk Factors for Obstructive Sleep Apnea in Adults. *JAMA.*2004;291(16):2013–2016. doi:10.1001/jama.291.16.2013

2. Benjafield AV, Ayas NT, Eastwood PR, et al. Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. *Lancet Respir Med*. 2019;7(8):687-698. doi:10.1016/S2213-2600(19)30198-5

3. Epstein LJ, Kristo D, Strollo PJ Jr, et al. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. *J Clin Sleep Med*. 2009;5(3):263-276.

4. Carvalho B, Hsia J, Capasso R. Surgical therapy of obstructive sleep apnea: a review. *Neurotherapeutics*. 2012;9(4):710-716. doi:10.1007/s13311-012-0141-x

5. Haskell B, Voor M, Roberts A. A consideration of factors affecting palliative oral appliance effectiveness for obstructive sleep apnea: a scoping review, Journal of Clinical Sleep Medicine, April 1, 2021, Vol. 17, No. 4 p. 833-848 https://doi.org/10.5664/jcsm.9018

6. Self-reported improvement in obstructive sleep apnea symptoms compared to treatment response with mandibular advancement device therapy: a retrospective study. Linda Sangalli L, Yanez-Regones F, et.al. Sleep and Breathing. https://doi.org/10.1007/s11325-022-02754-4

7. Haskell J, Haskell B, Spoon M, and Feng C. The relationship of vertical skeletofacial morphology to oropharyngeal airway shape using cone beam computed tomography: Possible implications for airway restriction The Angle Orthodontist: 2014, 84, (No. 3): 548-554

8. Liu Y, Lowe AA, Fleetham JA, Park YC. Cephalometric and physiologic predictors of the efficacy of an adjustable oral appliance for treating obstructive sleep apnea. Am J Orthod Dentofacial Orthop. 2001;120(6):6[39]–647.

9. Mostafiz W, Dalci O, Sutherland K, et al. Influence of oral and craniofacial dimensions on mandibular advancement splint treatment outcome in patients with obstructive sleep apnea. Chest. 2011;139(6):1331–1339.

10. Glupker L, Kula K, Parka E, Babler W, Stewart K, Ghoneima A, Three-dimensional computed tomography analysis of airway volume changes between open and closed jaw positions. AJO-DO 2015;147:426-434.

11. Oatis C. Mechanics and pathomechanics of swallowing. In CA Oatis, ed. Kinesiology: The Mechanics and Pathomechanics of Human Movement. Baltimore, MD: Lippincott, Williams and Wilkin; 2009: 423–437.

12. Rose EC, Barthlen GM, Staats R, Jonas IE. Therapeutic efficacy of an oral appliance in the treatment of obstructive sleep apnea: a 2-year follow-up. Am J Orthod Dentofacial Orthop. 2002;121(3):273–279.

13. Posselt U. Movement areas of the mandible. J Prosthet Dent. 1957;7(3): 375–385.

14. Haskell J, McCrillis J, Haskell B, Scheetz J, Scarfe W, Farman A. Effects of mandibular advancement device (MAD) on airway dimensions assessed with cone beam computed tomography. Semin Orthod. 2009;15(2):132–158.

15. Conley R, Cattaneo P, Haskell B. Characterization of the upper airway morphology and its changes in the apneic patient using cone beam computed. tomography. In: Kapila S, ed. Cone Beam Computed Tomography in Orthodontics Indications, Insights, and Innovations.1st ed. Oxford, UK: Wiley Blackwell; 2014, Chapter 13: 273–291.

16. Alves M Jr[1], Franzotti ES, Baratieri C, Nunes LK, Nojima LI, Ruellas AC. Evaluation of pharyngeal airway space amongst different skeletal patterns. Int J Oral Maxillofac Surg. 2012 Jul;41(7):814-9

17. Bilston L, Gandevia S. Biomechanical properties of the human upper airway and their effect on its behavior during breathing and in obstructive sleep apnea. J Appl Physiol 1985. 2014;116(3):314–324.

18. Melo S, Li Z, Kamburoglu K, Enciso R, Scarfe W. Obstructive sleep apnea/ hypopnea syndrome. In: Scarfe WC, Angelopoulos C, eds. Maxillofacial Cone Beam Computed Tomography Principles, Techniques and Clinical Applications. 1st ed. Oxford, UK: Springer; 2018:1–33.

19. Sutherland K, Chan ASL, Ngiam J, Dalci O, Darendeliler MA, Cistulli PA. Awake multimodal phenotyping for prediction of oral appliance treatment outcome. J Clin Sleep Med. 2018;14(11):1879–1887.

20. Jamieson A, Guilleminault C, Partinen M, Quera-Salva MA. Obstructive sleep apneic patients have craniomandibular abnormalities. Sleep 1986;9

21. Marras W. Biomechanics of the human body. In: Salvendy G, ed. Handbook of Humans Factors and Ergonomics. 1st ed. New York, NY: John Wiley and Sons; 1997; Chapter 9: 233–267.

22. W. Proffitt, Contemporary Orthodontics, Mosby, St. Louis, MO 2000, Chapter 6, Orthodontic Diagnosis p.177

23. Hagen–Poiseuille equation Hagen–Poiseuille equation - Wikipedia Accessed 23 March 2022

24. Chung F, et.al High STOP-Bang score indicates a high probability of obstructive sleep apnoea Br J Anaesth. 2012 May; 108(5): 768–775.

---

25. Chervin R, et al, Pediatric Sleep Questionnaire: validity and reliability of scales for sleep disordered breathing, snoring, sleepiness, and behavioral problems, Sleep Medicine 2000;1:21-32

26. Fernandez-Sanjuan P, Arrieta J, et. al. Optimizing Mandibular Advancement Maneuvers during Sleep Endoscopy with a titratable Positioner: DISE-SAM Protocol. Journal of Clinical Medicine 2022 11, 658. https://doi.org 10.3390/jcm11030658

27. Grauer D, Cevidanes LS, Styner MA, Ackerman JL, Proffit WR. Pharyngeal airway volume and shape from cone-beam computed tomography: relationship to facial morphology. Am J Orthod Dentofacial Orthop. 2009;136(6):805–814.

28. NejaimY, Aps JKM, Groppo FC, Haiter Neto F. Evaluation of pharyngeal space and its correlation with mandible and hyoid bone in patients with different skeletal classes and facial types. Am J Orthod Dentofacial Orthop. 2018;153(6):825–833.

29. Shen HL, Wen YW, Chen NH, Liao YF. Craniofacial morphologic predictors of oral appliance outcomes in patients with obstructive sleep apnea. J Am Dent Assoc. 2012;143(11):1209–1217.

---

30. Four Bar Linkage https://en.wikipedia.org/wiki/Four-bar_linkage Wikipedia Accessed 22 March 2022

31. Taranto-Montemurro L, Sands S, Edwards B, et al. Desipramine improves upper airway collapsibility and reduces OSA severity in patients with minimal muscle compensation. *Eur Respir J* 2016;48(5):1340-50.

32. Grace KP, Hughes SW, Horner RL. Identification of the mechanism mediating genioglossus muscle suppression in REM sleep. *Am J Respir Crit Care Med* 2013;187(3):311-9.

33. Kevin O'Brian's Orthodontic Blog. February 11, 2019. Part 2 of a brilliant summary of orthodontics and Obstructive Sleep Apnea. Accessed March 11, 2020 https://kevinobrienorthoblog.com/orthodontics-and-osa-part-2/.

34. Gray H, Goss CM (Ed.) Anatomy of the Human Body (Twenty-eighth Edition) Pgs. 152, 169-172, Lea and Fibiger, Philadelphia, May, 1969

Acknowledgement:

The authors thank Dr. WC Scarfe, Chair, Department of Diagnosis and Oral Health University of Louisville School of Dentistry for access to records.

Figure 1

Table 1

	GOOD RESPONDERS													POOR RESPONDERS														
	Data Measures													**Data Measures**											**ALL SUBJECTS**			
Subject	S8	S13	S18	S11	S6	S2	S24	S5	S16	S22	S1	AVG	STDEV	S3	S10	S17	S4	S9	S21	S14	S20	S12	AVG	STDEV	AVG	STDEV	p-value	
ANB (deg)	8.3	-0.6	-0.4	5	9.7	INSF	-0.1	4.6	-2.4	1.8	4.1	3.0	4.0	-1.7	6.2	3.0	1.1	5.1	-0.3	-2.5	4.9	3.9	2.2	3.2	2.59	3.56	0.31	
Wits (mm)	1.1	-10	-7.7	4.5	3.7	3.5	-1.7	2.4	-7.4	-3.3	1.7	-1.2	5.2	-8.4	-0.3	-5.0	1.0	-0.8	-3.1	-4.3	-0.9	-2.5	-2.7	2.9	-1.95	4.28	0.21	
ODI	74.9	54.8	52.6	68	74.1	75.8	72.7	86.1	56.8	72.2	80.4	69.9	10.8	63.1	66.5	64.2	74.9	68.9	65.9	57.9	64.2	77.5	67.0	6.0	68.43	8.88	0.23	
Delta mid. pharyngeal muscle	-1.7	-5.1	-3.9	-0.2	0.2	-2.5	0.5	-3.9	-3.4	-1.7	-0.9	-2.1	1.9	-5.3	-7.6	-1.5	-2.1	-3.2	-7.4	-1.4	2.0	2.0	-2.7	3.5	-2.39	2.69	0.31	
delta min axial airway %	154	65.9	64.6	61.8	59.4	52	47.1	42.5	33.9	22.4	18.9	56.6	36.3	13.2	12.0	7.6	2.3	2.3	2.9	-8.5	-15.7	-38.7	-2.5	16.4	27.05	41.42	0.00	****
AVG % airway change	56.6													-2.5											27%	41.79		

INSF- Insufficient data for measure

<u>Cephalometric and airway measurements.</u> “Good” responders are identified in green as subjects with greater than or equal to 16% minimal axial area airway increase with an OA in place. “Poor” responders in red were subjects with less than 16% minimal axial airway area increase with an OA in place. Change in the middle pharyngeal muscle length and minimal axial area were taken as the difference of measures with and without an OA in place.

Table 2

	Norm	One St Dev	Threshold	OAEI point value
ANB (deg)	2	3.5	>4	2
Wits (mm)	-1	1	>3	1
ODI	75	5	>70	3
Delta mid. pharyngeal muscle	-	-	>-3	2

Standardized cephalometric values and assigned point values for OAEI scoring. Three cephalometric variables selected received increasing OAEI point values based on the value of one standard deviation from previously established means except for Wits (3 SDs). As there is no current mean value for the length of the middle pharyngeal muscle length the median score was assigned as an OAEI point value.

Table 3

	OAEI *without* middle pharyngeal muscle measures: OAEI threshold ≥3																								ALL SUBJECTS			
Subject	S8	S13	S18	S11	S6	S2	S24	S5	S16	S22	S1	AVG	STDEV	S3	S10	S17	S4	S9	S21	S14	S20	S12	AVG	STDEV	AVG	STDEV	p-value	
ANB (deg)	2	0	0	2	2	0	0	2	0	0	2	0.9	1.0	0	2	0	0	2	0	0	2	0	0.7	1.0	0.79	1.01	0.30	
Wits (mm)	0	0	0	1	1	1	1	0	0	0	0	0.4	0.5	0	0	0	0	0	0	0	1	0	0.1	0.3	0.24	0.44	0.10	
ODI	3	0	0	0	3	3	3	3	0	3	3	1.9	1.5	0	0	0	3	0	0	0	0	3	0.7	1.3	1.29	1.53	0.03	*
OAEI score	**5**	**0**	**0**	**3**	**6**	**4**	**4**	**5**	**0**	**3**	**5**	3.2	2.2	**0**	**2**	**0**	**3**	**2**	**0**	**0**	**3**	**3**	1.4	1.4	2.31	2.06	0.02	*
OAEI score ≥3	y	n	n	y	y	y	y	y	n	y	y			n	n	n	y	n	n	n	y	y						
Successful prediction	8 out of 11													6 out of 9														
Successful prediction (%)	73													67														
Combined Accuracay	**(73%+67%)/2= 70% accuracy**																											

Scoring Criteria: ANB> 4, WITS > 3, ODI > 70

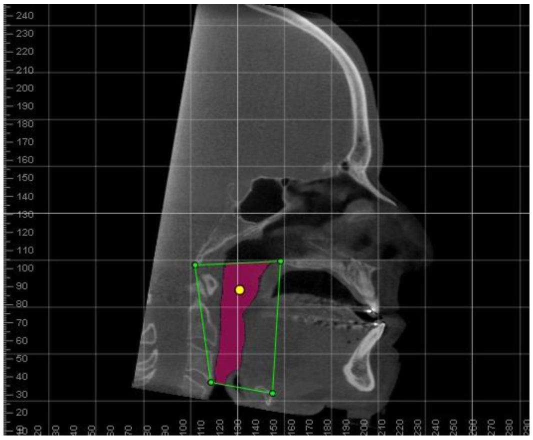
OAEI calculations without inclusion of the middle pharyngeal muscle length change. Both “good” and “poor” responder types were evaluated with the OAEI point scoring and compared to their expected response type. Eight of the eleven “good” good responder types matched their predictions (denoted by a green box with “y”) by achieving an OAEI score of greater than or equal to 3 yielding a 73% accuracy. Of the “poor” responders, six of nine were consistent with their response type (denoted by a red box with “n”) by obtaining an OAEI score of less than 3 yielding an accuracy rate of 67%. The pooled data from both responder types obtained 70% accuracy.

Table 4

	OAEI *with* mid. pharyngeal muscle measures: OAEI threshold ≥5																								**ALL SUBJECTS**			
Subject	S8	S13	S18	S11	S6	S2	S24	S5	S16	S22	S1	AVG	STDEV	S3	S10	S17	S4	S9	S21	S14	S20	S12	AVG	STDEV	AVG	STDEV	p-value	
ANB (deg)	2	0	0	2	2	0	0	2	0	0	2	0.9	1.0	0	2	0	0	2	0	0	2	0	0.7	1.0	0.79	1.01	0.30	
Wits (FOP) (mm)	0	0	0	1	1	1	1	0	0	0	0	0.4	0.5	0	0	0	0	0	0	0	1	0	0.1	0.3	0.24	0.44	0.10	
ODI	3	0	0	0	3	3	3	3	0	3	3	1.9	1.5	0	0	0	3	0	0	0	0	3	0.7	1.3	1.29	1.53	0.03	*
Delta mid. pharyngeal muscle	2	0	0	2	2	2	1	0	0	2	2	1.2	1.0	0	0	2	2	0	0	2	1	2	1.0	1.0	1.09	0.97	0.34	
OAEI score	**7**	**0**	**0**	**5**	**8**	**6**	**5**	**5**	**0**	**5**	**7**	4.4	3.0	**0**	**2**	**2**	**5**	**2**	**0**	**2**	**4**	**5**	2.4	1.9	3.40	2.67	0.05	*
OAEI Score ≥5	y	n	n	y	y	y	y	y	n	y	y			n	n	n	y	n	n	n	n	y						
Successful prediction	8 out of 11													7 out of 9														
Successful prediction (%)	73													78														
Combined Accuracay	**(78%+73%)/2= 75.5% accuracy**																											

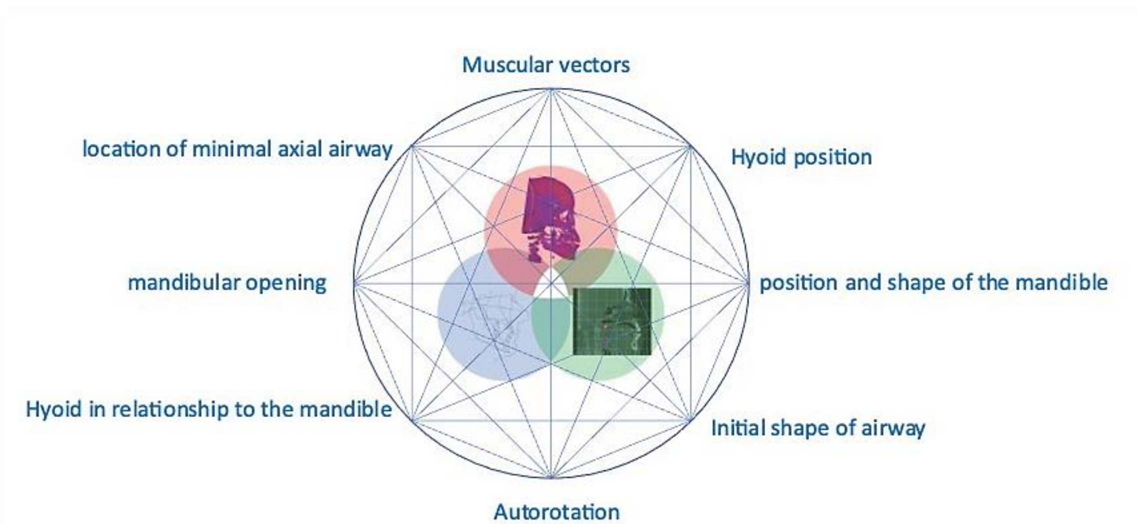
Scoring Criteria: ANB> 4, WITS > 3, ODI > 70, Change in mid. pharyngeal muscle length > -3.

<u>OAEI calculations including the middle pharyngeal muscle length change</u>. Both "good" and "poor" responder types were evaluated with the OAEI point scoring and compared to their expected response type. Eight of the eleven "good" good responder types matched their predictions (denoted by a green box with "y") by achieving an OAEI score of greater than or equal to 5 yielding a 73% accuracy. Of the "poor" responders, seven of nine were consistent with their response type (denoted by a red box with "n") by obtaining an OAEI score of less than 5 yielding an accuracy rate of 78%. The pooled data from both responder types obtained 75.5% accuracy.



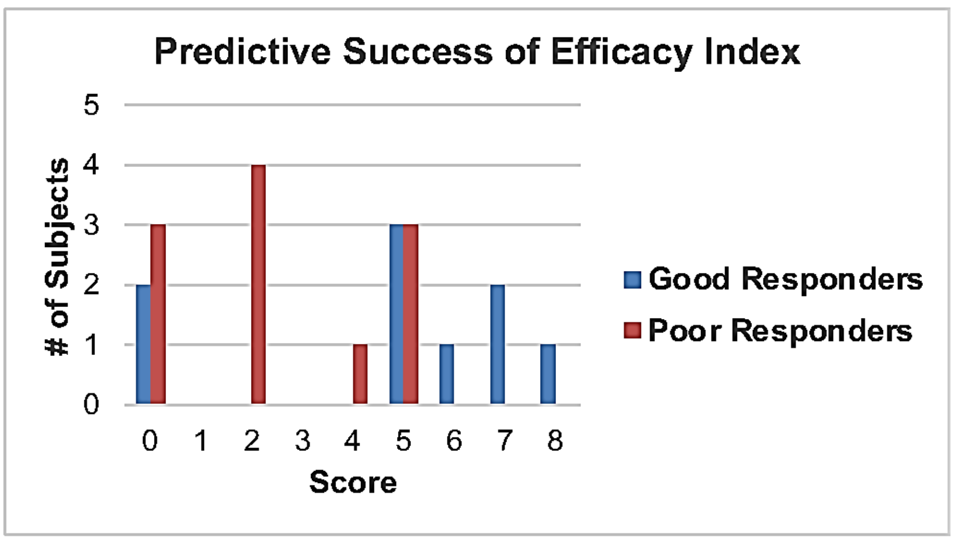
Airway capture and constructed borders. CBCT images display a green box with vertices at the following points: posterior nasal spine, basion, the anterior-inferior border of the third cervical vertebral body and the central body of the hyoid bone. Sagittal perspective of airway borders and seed point (yellow dot) to define airway rendering.

Figure 2



The interactive nature of airway patency. At least 36 possible interactions are noted for muscle vectors, skeletal anatomy, jaw position, and airway lumen.

Figure 3



A distribution of subjects according to OAEI score. "Good" anatomic responders (blue) are located at the highest scoring end of the distribution with two outliers that scored zero points. "Poor" anatomic responders (red) have lower scores on average; being found at the lower end of the score table.

Figure 4

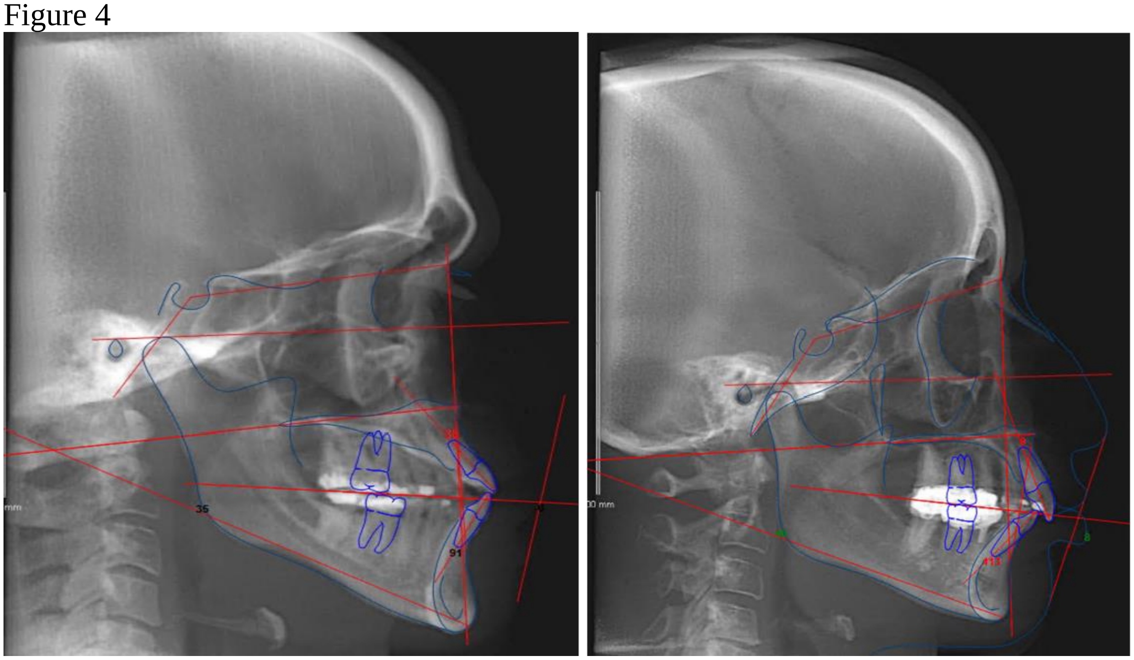
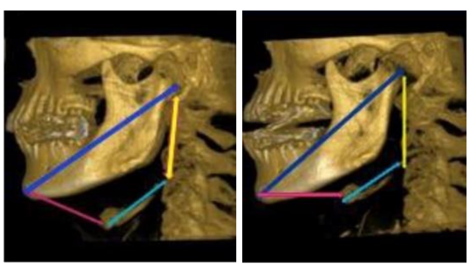


Figure 4a Figure 4b

Examples of Outlier and Non-Outlier Good Responders Figure 4a: Good Responder Outlier with a poor OAEI Score. (Class III tendency) Figure 4b: Good Responder with a good OAEI score. (Class II tendency) The airway appears small with Class II characteristics (b), Dimensions of the oro-pharynx may be larger in prognathic types (a).

Figure 5



A. B.

<u>Four-Bar Analysis with and without OA in place</u>. A four-bar closed chain linkage with bars and four joints with three degrees of freedom using straight-line 2-D vectors moving in parallel. (A) Without OA. Geniohyoid muscle (red): mandibular genial tubercles to hyoid. Hyoid bone (light blue). The middle pharyngeal muscle vector (yellow) from the pharyngeal tubercle of occipital bone to anterior of styloid process / posterior portion of hyoid. Mandible - (dark blue) to pharyngeal tubercle. The links move in parallel. (B) With OA. (C) CBCT of Middle Pharyngeal Constrictor vector.

C.

ORAL APPLIANCE EFFICACY APPENDIX :

Appendix 1: Cephalometric terminology

ANB: A point, or “subspinale” is the maxillary apical base, or deepest concavity anteriorly on the maxillary alveolus. N point or “Nasion” is the most anterior point of the frontonasal suture as seen from the lateral perspective on a head film. B point, or “supramentale” is the deepest concavity anteriorly on the mandibular symphysis. The ANB angle illustrates how the maxilla and mandible relate in position to one another.
WITS: Measures the severity or degree of anteroposterior jaw discrepancy by drawing perpendiculars from points A and B on the maxilla and mandible to the occlusal plane. The distance between the two vertical lines on the occlusal plane illustrates the discrepancy. A positive WITS measure has the mandible behind the maxilla, while a negative WITS shows a protrusive mandibular base.
ODI: Describes a skeletal tendency towards open bite or deep bite. ODI is the sum of two angles showing correlation with incisor overbite, illustrating the difference between deep bite and normal overbite, and deep bite compared to open bite. It is the sum of two angles (AB-Mandibular Plane and Palatal Plane-Frankfort Horizontal). For pictorial examples see reference below.

Middle Pharyngeal Muscle Vector Measure: The vector runs from the pharyngeal tubercle of the occipital bone, anterior to styloid process to the greater and lesser cornu of the hyoid at the posterior of the hyoid. (Figure 5 C)

Fatima F, Fida M, Shaikh, A Reliability of overbite depth indicator (ODI) and anteroposterior dysplasia indicator (APDI) in the assessment of different vertical and sagittal dental malocclusions: a receiver operating characteristic (ROC) analysis *Dental Press J Orthod.* 2016 Sep-Oct; 21(5): 75–81. doi: 10.1590/2177-6709.21.5.075-081.oar

Appendix 2:

ORAL APPLIANCE EFFICACY INDEX WORKSHEET:

Not including change in middle pharyngeal muscle length

Required Measures

ANB

Wits

ODI

If value is within box, circle score and total below.

Measured Value	Observed Value		Score
ANB	1…2…3	4…5…6…7…or greater	2
Wits	0…1…2	3…4…5…6…or greater	1
ODI	67…68…69	70…71…72…or greater	3

TOTAL

POOR RESPONDER — GOOD RESPONDER

0 1 2 — **3 4 5 6 7 8**

70% predicted accuracy

of ≥16% minimal axial airway area increase

Appendix 3:

ORAL APPLIANCE EFFICACY INDEX WORKSHEET:

Including change in middle pharyngeal muscle length

Required Measures

ANB

Wits

ODI

Middle Pharyngeal Muscle Length Change

If value is within box, circle score and total below.

Measured Value	Observed Value		Score
ANB	1…2…3	4…5…6…7…or greater	**2**
Wits	0…1…2	3…4…5…6…or greater	**1**
ODI	67…68…69	70…71…72…or greater	**3**
Δ Mid. Pharyngeal Muscle Length	-6…-5…-4	-3…-2…-1…0…or greater	**2**

TOTAL

POOR RESPONDER

0 1 2 3 4

GOOD RESPONDER

5 6 7 8

75.5% predicted accuracy

of ≥16% minimal axial airway area increase