Oropharyngeal dimensional changes following maxillary expansion with two different appliances: a CBCT study

By

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ABSTRACT

Maxillary expansion is used to correct maxillary deficiencies, the most common technique is the Rapid Maxillary Expansion. Although there are several other treatment types depending on age such as surgery or archwire; maxillary expansion, have been related to the increase of the upper airway volume and minimal cross-sectional area (MCA). However, contradictory results regarding the measured changes in the oropharyngeal portion of upper airway have led to uncertainty about the real effect of maxillary expansion on the oropharynx dimensions.

Moreover, there is no published research regarding oropharyngeal dimensional changes after the application of Damon philosophical treatment approach. Following the claim from Damon proponents that the therapeutic effect after its use in the constricted maxilla is a broader dental arch due to alveolar bone remodeling. We speculate if the oropharyngeal volume and MCA could also be increased. Therefore, the main objective of this study is to compare the volume and MCA changes in the oropharyngeal space following maxillary expansion using the Damon system versus Hyrax appliances, assessed through CBCT imaging.

A retrospective analysis of data from a randomized parallel clinical controlled trial with an allocation ratio of 1:1 was conducted. Patients between 11 to 17 years old, with maxillary transverse discrepancies in need of maxillary expansion, were included and randomly allocated into one of two treatment groups, Hyrax or Damon, in the orthodontic clinic at the University of Alberta, Edmonton Canada. Patients underwent CBCT imaging at three time-points: T1- before treatment and after clinical evaluation, to further evaluate and assist the clinicians on the diagnosis on dental and craniofacial orthodontic discrepancies; T2- at 6 months, and T3- after completion of all orthodontic treatment. The CBCT data was assessed through Invivo Software (Anatomage, San Jose, California, US) and Dolphin Software (Dolphin Imaging & Management Solutions, Chatsworth, California US). Reliability of measurements was done to certify the reproducibility of the research. In addition, a qualitative assessment of breathing function was done using the NOSE questionnaire modified from The NOSE Scale 2003 developed by the American Academy of Otolaryngology-Head and Neck Surgery Foundation. Repeated measures multivariate analysis of variance (MANOVA) and Bonferroni post-hoc tests were used to analyse the differences between the treatment groups at each time-point and each software. A paired-sample t-test was applied to verify whether or not the changes were statistically significant. All the statistical analysis was made at a 5% significance level (95% CI) using IBM SPSS statistics 25 version (SPSS Inc, Chicago, IL).

A reliability assessment was done evaluating intra-reliability and inter-reliability with a second examiner. All results ranged above the excellent range of 90%. Our study showed a statistically significant increase in the oropharyngeal volume after 6 months maxillary expansion (T2), and after the completion of treatment (T3) when the oropharyngeal volume was evaluated in the Hyrax group with both software. Also, results showed a statistically significant increase in the MCA in the Hyrax group when evaluated with Dolphin software. The Invivo and Dolphin software showed they are statistically different when oropharyngeal dimensions were compared. Our results on the NOSE questionnaire showed no statistically significant improvement in breathing between time-points in both treatment groups. Future research should focus on airway function to correlate the dimensional changes to airflow and respiratory capacity function after maxillary expansion

treatment. As well, the qualitative analysis with patient's feedback by questionnaire could elucidate the patient's breathing improvement after orthodontic therapy.

PREFACE

This thesis is an original work of Silvia Patricio Gianoni Capenakas. The research project of which this thesis is a part received research ethics approval from the University of Alberta Research Ethics Board under the project named, "Analysis of Skeletal and Dental Changes obtained from a traditional Tooth-Borne Maxillary Expansion Appliance compared to the Damon system assessed through Digital Volumetric Imaging", number Pro00013379.

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LIST OF ABBREVIATIONS

2D – Two-dimensional

3D – Three-dimensional

AHI – Apnea/Hypopnea Index

AP – Anteroposterior

AR – Acoustic Rhinometry

BMI – Body Mass Index

CBCT – Cone Beam Computed Tomography

CIHR – Canadian Institutes of Health Research

CT – Computed Tomography

DICOM – Digital Imaging and Communications in Medicine

EEG – Electroencephalogram

EMG – Electromyography

ENT – Ear Nose and Throat specialist

EOG - Electrooculography

FOV – Field of View

HSAT – Home sleep apnea testing

HU – Hounsfield Unit

ICC – Intraclass Correlation Coefficient

ICSD-3 – International Classification of Sleep Disorders-third edition

kVp – Peak kilovoltage

mAs – Milliamperage seconds

MCA – Minimal cross-sectional area

MDCT – Multidetector Computed Tomography

MRI – Magnetic Resonance Imaging

nPSG – Nocturnal Polysomnography

OSA – Obstructive Sleep Apnea

PRISMA-P – Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols

PSG – Polysomnography

RME – Rapid maxillary expansion

SBD – Sleep Breathing Disorder

SME – Slow maxillary expansion

T – Timepoint

LIST OF APPENDICES

Chapter 1: Introduction of concepts

1.1 Upper airway

1.1.1 Anatomy

The upper airway tract is part of the respiratory system and comprises the nasal cavity, oral cavity, and pharynx.[1] Its function includes air warming and humidification, defense against infections, protection from food aspiration, ventilation, swallowing, and speech.[1]

The nasal cavity comprises the nostrils, nasal septum and turbinates. It is the primary air entrance in inspiration and is responsible for thermic regulation warming and humidifying it. The nostrils are the two external openings. Right behind the nostrils, the nasal septum separates the two air passages and the choanae. The turbinates are bone curled shelves within the passageway in which the thermic regulations occur.

The oral cavity includes the teeth and periodontal tissues, the hard and soft palates and the tongue and floor of the mouth. The posterior boundary is the pharynx. The pharynx is a tubular organ connecting the nasal cavity, oral cavity, larynx, and esophagus. It is divided into nasopharynx, oropharynx, and hypopharynx. As only the nasopharynx and oropharynx are pertinent to this topic, a detailed description will solely be provided for them.

- The nasopharynx is the most superior part of the pharynx its boundary is the posterior edge of the nasal turbinates to the hard palate, bounded by the soft palate and palatopharyngeal arches and the posterior wall of the pharynx.[2,3] The nasopharynx communicates with the nasal cavities through the nasal choanae and with the middle ear through the Eustachian tube. The pharyngeal tonsils or adenoids are located in the posterior wall at the roof of the nasopharynx.

- The oropharynx has its boundaries as the base of the tongue (anterior wall), palatine tonsils and tonsillar pillars (lateral walls) and epiglottis (inferior boundary), posterior wall of the pharynx (posteriorly). The oropharynx can be divided into retropalatal (also called velopharynx), with the boundaries from the hard palate to the caudal margin of the soft palate, and retroglossal, from the caudal margin of the soft palate to the base of the epiglottis.[2]
- The hypopharynx links the oropharynx to the esophagus from the epiglottis.

1.2 Relationship between upper airway and craniofacial structures

The term airway space refers to the air passage from the nose or mouth to the lungs. More specifically, the upper airway is responsible for speech, swallowing and part of the respiratory functions. Swallowing and deglutition demand the sealing of the nasopharyngeal airway, and vocalization requires coordination of larynx and nasopharynx structures.[4] Besides swallowing and deglutition, the pharyngeal airway space should be open all times, and its patency is in large part controlled by the neuromuscular system.[4] However during sleep, there is a decrease in the neuromotor output to pharyngeal muscles, and this works in favour of potential pharyngeal collapsibility.[4] The patients diagnosed with Obstructive Sleep Apnea (OSA) usually present narrowed upper airway during sleep in the retropalatal and/or retroglossal regions.[4]

1.2.1 Craniofacial structures and airway function

The anteroposterior (AP), transversal and vertical dimension of the airway have "a proportional relationship to the jaw and facial growth patterns".[5,6] Doyle and Swarts described the bihamular distance as "the linear distance between the outer margins of the bilateral hamular processes of the medial pterygoid plate which is an approximate measure of palatal width".[7] The transversal pharyngeal growth (bihamular distance) appears to level off around the 24 months of life, however the distance between the pterygoid plates increases until maturity.[6] The normal mandibular and maxillary growth pattern with a counter-clockwise rotation might induce to larger airway dimension because the cranial base shape (nasion-sella-basion) with an acute angle influences the vertical direction of the pharyngeal growth.[5,6] In other words, facial growth affects the size and shape of the upper airway space.[8] While craniofacial hard and soft tissues are growing during childhood and adolescence, the lymphoid tissue is diminishing, leading to an increase in the upper airway dimensions.[8] This event was first described by Scammon et al, where the lymphoid (tonsils and adenoids) masses increase fast during the early ages, with a slower development thereafter, a peak before adolescence and a decrease to adult.[6,9] The anterior cranial base grows in length (AP) up to seven years old, and the posterior cranial base up to 13 years old (AP and transverse); concurrently the nasomaxillary complex moves forward, and the midface bones move anteriorly and inferiorly.[8] Meanwhile the mandible increases forward and downward by adding bone on the posterior and superior edges of the ramus. All these events will enlarge pharyngeal height and width.[8]

Antagonistically, a great decrease of nasal airflow may lead to changes in craniofacial features as a lower and forwarded position of the tongue, lower position of the hyoid bone, short upper lip, prominent upper incisors, increase of mouth breathing over nasal breathing, anteriorly position of head and neck, increase in the anterior face height, increase in the mandibular and occlusal plane angles, high palatal vault, class II malocclusion, clockwise facial growth pattern, posterior crossbite and narrowed maxillary arch among others.[5,10–12] These features usually facilitate morphological changes associated with a face phenotype known as adenoidal facies. However, there is a dilemma of who can first, the decrease in nasal flow lead to craniofacial changes and compensations or the craniofacial deficient growth lead to an increase in nasal resistance?[7]

1.3 Sleep-breathing disorders in children

The International Classification of Sleep Disorders- third edition (ICSD-3) updated in 2014 allowed better communication worldwide regarding sleep disorders, not only for research purposes but also for diagnosis and epidemiology standardisation.[13] The ICDS-3 classification has primary categories such as insomnias, sleep-related breathing disorders (in which Obstructive Sleep Apnea is one of the sub-categories), hypersomnia of central origin, circadian rhythm sleep disorders, sleep-related movement disorders, parasomnias, and other sleep disorders.[4,13] The major sleep disorders in children are Obstructive Sleep Apnea (OSA), periodic leg movements of sleep, narcolepsy, primary insomnia, and delayed sleep phase syndrome.[14]

The OSA is related to an obstruction in the airway resulting in increased airflow resistance.[4,13] The OSA is characterised by repetitive episodes of complete or partial cessation in breathing.[4,13] Often it is associated with a decreased blood oxygen saturation.[4] Snoring, sleep disruption, daytime sleepiness, insomnia are commonly associated.[4,13] In children, the diagnosis requirements are at least one event of Apnea/Hypopnea Index (AHI), at least two respiratory cycles' duration, per hour of sleep.[4,13] Aggravated sleep-breathing problems in children generally involve lymphoid tissue hyperplasia.[8] Obesity, is a significant risk factor for pediatric OSA.[8] Untreated

OSA may lead to growth impairment; on the other hand, mandibular retrognathia, long and narrow faces, narrow and deep palate, may increase the risk for OSA in children.[8] OSA prevalence in children is accounted to be around 1 to 4 %.[8] Only the physician can diagnose OSA. However, the dentists have an important role in screening for sleep disorders breathing, applying, and managing oral appliances when indicated.[8]

1.4 Evaluating upper airway dimensions

1.4.1 2D Cephalometric radiograph

The two-dimensional (2D) cephalometric radiography favours the craniofacial morphology and growth 2D analysis.[15] However, even though there are two possibilities of this type of radiography, which are the lateral cephalometric radiographs and the postero-anterior cephalometric radiographs, there is limited information of the mediolateral oropharyngeal airway dimensions that does not enable reliable information on the volume and minimal cross-sectional area (MCA).[8,15] The 2D re-presentation of a three-dimensional (3D) structure incurs in distortion, differences in magnifications, projective displacements, rotational errors, and superimposition of the bilateral craniofacial structures.[16–19]

1.4.2 Magnetic Resonance Imaging (MRI)

MRI uses a magnetic field to manipulate hydrogen ions presented in the body creating static and dynamic 3D images.[20,21] MRI has high tissue contrast, high sensitivity, and specificity for the generated images.[21] The volumetric MRI approach enables the acquisition of volumetric data of organs and systems, allowing quantitative information of some airway risk factors.[21,22] The MRI has a high accuracy for soft tissue representation. However, cost and accessibility are the disadvantages of this imaging technique.

1.4.3 Nasopharyngoscopy

Nasopharyngoscopy is a non-radiation exposure minimally invasive exam; it uses a flexible tube to evaluate airway lumen and obstruction.[2] It is mostly used by Ear Nose and Throat (ENT) specialists to analyse nasal passage, pharynx and vocal cords.[2] It can be performed in the supine or sitting positions; during wakefulness and sleep.[2] However, no estimation on dimensions can be made.[23]

1.4.4 Rhinomanometry

Rhinomanometry evaluates nasal flow and pressure using pressure transducers and miniaturised technology.[21] However, it cannot identify the likely position of obstruction.[23]

1.4.5 Acoustic rhinometry (AR)

It is a non-invasive technique for assessing airway cross-sectional area as a function of airway distance.[4] It is based on the study of the sound wave reflected from the respiratory tract.[2] The acoustic reflection combines the determination of upper airway patency using Rhinomanometry for nasal airway and pharyngometry for pharynx; both are connected to a monitor which display cross-sectional area and volume at different points of the airway.[21,24] This method do not use ionising radiation exposure.[21] Easily available for ENT, but not a commonly assessable tool for orthodontists.

1.4.6 Nocturnal Polysomnography (nPSG)

The nPSG is considered to be the gold standard for evaluation of sleep, pulmonary sleep medicine, and neurology.[14] The Polysomnography (PSG) is composed of three main measures: electroencephalography, electromyography, and electrooculography, respectively the analysis of brain, motor, and eye activities.[14] Additionally, other electrophysiological measures are gathered: electrocardiograms and nasal/oral airflow.[14] Those measurements are complementary; the electro-encephalogram (EEG) is the core of the PSG with the measurement of the electrical activity of the brain[14]. "EEG is a continuous variance in voltage over time where the source potential for the voltage is derived from the slow potential activity of the dendrites and somas residing within the first three layers of the cortex."[14] The fifth stage of sleep (the so-called third stage of consciousness) cannot be accurately observed through the EEG; at this stage, the rapid eye movements and the absence of muscle tone are two important characteristics, for this reason, the electrooculography (EOG) and the electromyography (EMG) measures are essential.[14] The measure of respiratory function is complex because this appraisal depends upon airflow, respiratory effort, and degree of arterial blood oxygenation.[14] In the case of oral/nasal airflow, the measurement occurs based on the temperature changes of air inhaled and exhaled.[14] The changes in temperature modulate the conductivity of an exogenous voltage generated by crossing different metals within a small sensor.[14] The cooler air makes the metals conduct more signals; warmer air makes it conduct fewer signals, then an oscillating voltage is created.[14] To measure the respiratory effort, the expansion and contraction of the chest inflect the conductivity of an exogenous voltage through an elastic full of metal particulate. With the movement of the chest, the metal particles pull apart, and the signals turn to be less when the metal particles draw near, there is more signal passing, it creates an oscillating voltage.[14] The blood oxygenation or oximetry measurement occurs with a photosensitive sensor being placed in one side of a highly vascularized area (usually ear lobe) and a light beam is applied on the other side.[14] This process allows the light to pass through the tissue to be measured. The light signal is transformed into a voltage. [14] The more light passes, the more oxygenated the blood, then an oscillating voltage is produced.[14]

nPSG is the gold standard exam for OSA's diagnostic purposes, both in children and adult.[8,25] However, there is a variation on the interpretation of the PSG results and the criteria for the definition of OSA in children.[26] IN children the protocol for OSA diagnosis varies from ≥ 5 AHI; at least one event of, at least two respiratory cycles' duration, per hour of sleep; or 1-5 AHI/hour as mild, 5-10 AHI/hour as moderate and ≥ 10 AHI/hour as severe.[4,8,13]

1.4.7 Home sleep apnea testing (HSAT)

Due to the fact that in-lab PSG are expensive, often not readily available and have the inconvenience of spending the night in the lab; the home sleep apnea testing is a possibility to evaluate sleep-breathing disorders.[27] The HSAT is a well-accepted exam when evaluating adults for the sleep-breathing disorder, however, a good correlation to PSG results is controversial and problems with sensitivity and specificity have been reported.[8,27] However, in children the results have not demonstrated a good correlation as in adults; both single channel (type 4) and 4-7 channels (type 3) studies have shown a poor correlation to PSG results in .[27–29]

1.4.8 Computed Tomography (CT) and Cone Beam Computed Tomography (CBCT)

The CT was first developed in the 1970s revolutionizing how imaging exams allowed the 3D visualization of body structures.[17] CT uses a fan beam transmitting the radiation in the form of a helix or spiral, producing the images by slices, while the CBCT.[17] However, the high cost and high radiation dose made the use of CT to craniofacial imaging limited.[17] In the late 1990s, the CBCT was created using a beam in the shape of a cone, enabling the capture of the images with one or two rotations, decreasing radiation and time to scan. [17,30,31] The CBCT scan produces multiple consecutive planar images.[31,32]

The CBCT scan allows the diagnostic and morphometric analysis of hard and soft tissue and may be used to assess the airway and surrounding structures, only when available at the dentist's office, to evaluate and monitor upper airway changes after orthodontic treatments.[8] The 2D visualization of the three planes (sagittal, axial and coronal) is possible and a 3D rendering volumetric model reveals all the craniofacial structures and anatomy details enhancing the evaluation of dental, skeletal and upper airway anatomy.[17] Some studies have validated the CBCT's linear, angular, area and oropharyngeal volumetric measurement accuracy and reliability to examine airway.[21,33–35] A recent systematic review evaluating CBCT reliability to analyse upper airway concluded that the upper airway dimension acquisition may vary depending on the experience of the examiner; the oropharynx dimensions had the less variability on the results and the higher reliability.[36] Even though it is an acceptable method for upper airway analysis, no radiographic exam presents a high enough sensitivity and sensibility to be used alone as a risk assessment tool for OSA as it does not give information on neuromuscular tone, collapsibility trend and upper airway function.[8] One other limitation is the fact that imaging is done in a standing position which does not enable the analysis of the upper airway in a supine position which simulates the body sleeping position.[8] Also, CBCTs are not a good exam to evaluate soft tissue.

The difference in radiation dose between CT and CBCT is significant, depending on several factors as the field of view (FOV), milliamperage seconds (mAs), peak kilovoltage (kVp), beam filtration, and the number of images.[17,37] The radiation dose from a CBCT is higher than the conventional intraoral radiograph or a panoramic, although lower than the CT. [17,37] The dose is dependent on equipment type and exposure parameters.[37]

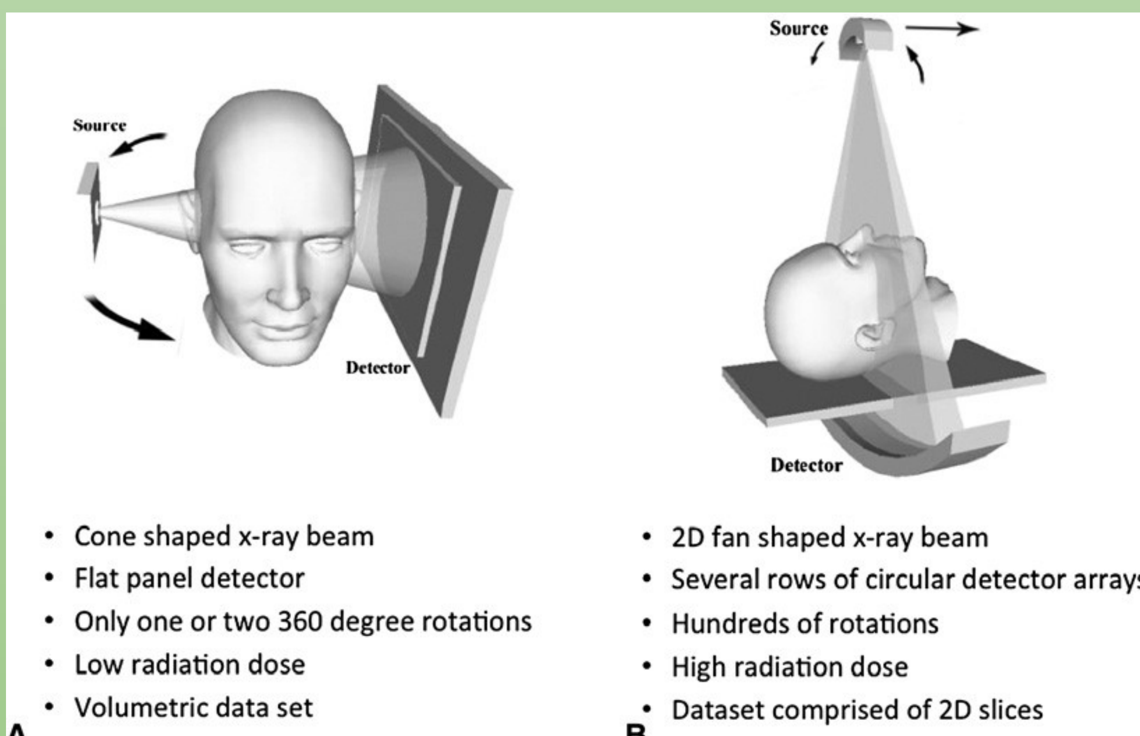


Figure 1: Representation of (A) CBCT and (B) CT and differences between them. (Kapilla, 2014 and Miracle and Mukherji, 2009)[17,38]

1.5 CBCT segmentation software

The CBCT image acquisition requires software to convert the Digital Imaging and Communications in Medicine (DICOM) files into 3D volumetric data; this process is called segmentation.[39] The segmentation can be manual or automatic/semi-automatic.[39] In the manual, the segmentation is made slice by slice prior to allow the software to merge into a 3D model.[39] In the automatic/semi-automatic, the examiner places the boundaries and defines the grey-levels, and then the software builds up the volume.[39] The manual processing is time-consuming when compared to the automatic/semi-automatic; however, studies have demonstrated that manual segmentation is more accurate than automatic/semi-automatic segmentation.[39,40] Some examples of manual software are OrthoSegment (Developed by the Orthodontic department at Case Western Reserve University, Cleveland, Ohio) and ONpharynx. Examples of automatic segmentation software are Dolphin (Dolphin Imaging & Management Solutions, Chatsworth, California), InVivo (Anatomage, San Jose, California), Mimics (Materialise, Leuven, Belgium), INTAGE, InsightSNAP (Cognitica, Philadelphia, PA), OnDemand (CyberMed, Seoul, Korea), 3dmdVultus (3dMD LLC, Atlanta, Georgia). El and Palomo tested various software and concluded that among others, InVivo and Dolphin were reproducible.[41] Another study showed that the manual segmentation is more accurate and reliable to evaluate upper airway following Le Fort III osteotomy.[42]

1.6 Maxillary constriction correction and its effects on airway

1.6.1 Maxillary expansion

The maxillary expansion is an orthodontic or orthopaedic treatment largely necessary in the correction of unilateral or bilateral crossbite, transversal constricted maxilla, and increase of dental arch perimeter.[43] Moreover, according to McNamara, not only the presence of crossbite indicates a narrow maxilla, but also a narrow maxillary intermolar distance without crossbites can imply the need for maxillary expansion.[44] Even though the primary aim of the maxillary expansion is to open the mid-palatal suture, studies have shown that the results of maxillary expansion come from skeletal expansion, alveolar bending and dental tipping.[45–48] The amount of those effects will depend on the type of appliance used to expand the maxilla. Maxillary expansion can be achieved by orthopaedic appliances, orthodontic appliances, and maxillofacial surgery.[49–51] Early diagnosis may favour early correction with orthopaedic appliances.[45] Since there is an increase in the palatal width, several studies have been evaluating the changes in airway dimensions, nasal width, and decrease in airway resistance.[52–56]

It has been shown that, anatomically, the nasal cavity increases in width after rapid maxillary expansion and can present a reduced air resistance.[23,57–62] However, there are controversies on clinical significance.[45]

1.6.2 Types of appliances

In general terms, there are four different methods to manage the transversal maxillary constriction: Slow maxillary expansion (SME), Rapid maxillary expansion (RME), surgically assisted maxillary expansion and fixed orthodontic wires. Among them, there are numerous treatment types and different appliances to correct the transversal constricted maxilla, mainly the decision between them is based on the patient's age/skeletal maturation.[45]

Orthopaedic appliances

The SME and RME are orthopaedic treatments. Usually, SME is used in early-aged children with primary or mixed dentition. The appliance of choice is banded continuous wire expanders such as Quad helix, while RME in older children and teenagers have banded jackscrew expanders such as Hyrax or Haas.[45] Among the various types of RMEs, the Hyrax is one of the most common orthopaedic appliances. Several studies have shown an increase in the nasal volume after RME,[63–65] and some studies have demonstrated oropharyngeal volume increase after the use of Hyrax to expand the maxilla,[60,62,66] although there were negative results for the increase of oropharynx after maxillary expansion using Hyrax.[65,67]

Orthodontic appliances

The orthodontic alignment can manage less severe cases of maxillary constriction. The Damon self-ligating system is an orthodontic philosophy that is also used to fix transversal discrepancies.[68] According to proponents of Damon philosophy, considerable expansion can be achieved in the buccal segments, producing a broader arch form.[68–70] Atik and Ciger concluded in their study that despite the absence of an active expansion appliance in the Damon group studied, an increase of the intermolar width similar to that in the conventional group using a quad-helix appliance emphasizes that the Damon system can expand the dental arch without using an auxiliary expansion appliance before fixed appliance therapy.[68]

1.7 Statement of the problem

Since the orthodontist has regular contact with children and knowledge on craniofacial growth and development, the screening for children at high risk of sleep-breathing disorders, more specifically OSA, is important, and in selected cases, if indicated by the leading physician, the orthodontist can contribute as part of the multidisciplinary team to manage OSA children.[8,71] The orthodontic treatment planning should be focused on the occlusion and skeletal discrepancy correction; however, the primary correction may contribute to the decrease of upper airway resistance as suggested in some studies after maxillary expansion and mandibular advancement.[8,60,62]

After maxillary expansion, the separation of the maxillary halves occurs followed by the separation of the nasal walls and lowering of the palate vault.[72] The transverse changes in the maxillary halves and consequently on the nasal walls after the maxillary expansion procedure seems to be directly related to the nasal cavity dimensional changes.[72–75] Better tongue position and stimulus for normal positioning of the mandible after the maxillary teeth repositioning are also described as a result of maxillary width expansion.[54] A hypothesis has been described as a reason for oropharyngeal changes: the "new" position of the tongue after maxillary expansion with more room in the oral cavity could be related to increases in the oropharyngeal retroglossal space[76]. In addition, the widening of the mandibular arch following the new maxillary posterior teeth position could increase the retropalatal space.

Several studies have shown an increase in the nasal cavity dimensions after RME; however, only a few studies have evaluated dimensional oropharyngeal changes after the maxillary constriction correction using RME.[61,76–79] Moreover, among them, the results vary widely. Additionally, the Damon System philosophy proponents claim the effectiveness of this system in expanding constricted maxillary arches. This claim has not been explored enough yet. Based on that, we aim to evaluate and compare oropharyngeal volumetric and minimum cross-sectional area changes after maxillary expansion using either Hyrax or Damon System and correlate the results with a questionnaire to subjectively check on patients' perceived breathing capacity. Furthermore, we wish to analyse the results by using two automated software for CBCT analysis. Reliability of the results will be done to appraise their reproducibility.

1.8 Research question and Hypothesis

The research questions for this study are:

1- Are the examiners reliable to evaluate the oropharyngeal volume and minimal cross-sectional area (MCA) using the software Invivo and Dolphin?
2- Are there differences in the Oropharyngeal measurements between Invivo and Dolphin?
3- Are there changes in oropharyngeal volume and the MCA between Time-point (T), T1, T2, and T3 in patients undergoing treatment with Hyrax significant?
4- Are there changes in oropharyngeal volume and the MCA between T1, T2, and T3 in patients undergoing treatment with Damon Appliance philosophy significant?
5- Are there differences in changes in oropharyngeal volume and MCA in patients undergoing treatment with Damon Appliance philosophy versus Hyrax significant?
6- Are there significant perceived changes using NOSE questionnaire?

The hypotheses are:

Reliability: H_{01A}: μ Examiner 1 (SG-C) = μ Examiner 1 (SG-C).

Reliability: H_{01B}: μ Examiner 1 (SG-C) = μ Examiner 2 (FA).

H_{O2}: μ Invivo = μ Dolphin. There is no difference in the mean oropharyngeal volume and/or MCA amongst software.

H_{O3}: Hyrax treatment μ T1= μ T2= μ T3. In other words, there are no differences in the mean oropharyngeal volume and/or MCA amongst the different time points T1, T2, T3 in patients treated with Hyrax.

H_{O4} : Damon System approach treatment μ T1= μ T2= μ T3. In other words, there are no differences in the mean oropharyngeal volume and/or MCA amongst the different time points T1, T2, T3 in patients treated with Damon.

H_{O5}: μ Hyrax = μ Damon System approach. There is no difference in the mean oropharyngeal volume and/or MCA between treatments.

H_{06}: μ NOSE results before maxillary expansion = μ NOSE results after maxillary expansion. There is no difference in the mean NOSE answers before and after treatment.

Chapter 2: Rapid maxillary expansion effects to the upper airway dimension and function in growing patients: an umbrella review

2.1 Introduction

The upper airway is part of the respiratory system and comprises a nasal cavity, oral cavity, and pharynx.[1] Upper airway's function includes air warming and humidification, defense against infection, protection from food aspiration, ventilation, swallowing, and speech.[1] Upper airway volume variation after orthodontic treatment has been heavily studied, but still has several inconsistencies due to differences in methodology and a large number of orthodontic/ orthopaedic appliances tested.

Maxillary expansion is used to correct maxillary deficiencies commonly related to posterior crossbites and crowding.[80] The most common technique used in mixed dentition is the rapid maxillary expansion (RME) with a tooth-anchor expander (Hyrax and Haas).[80] After maxillary expansion, the separation of the maxillary halves occurs followed by the separation of the nasal walls and lowering of the palate vault.[72] Additional reported changes related to the maxillary expansion are stretching of the tensor palatine muscles and improving the drainage of Eustachian tubes, reducing otitis media and conductive hearing loss.[72,73] In addition to those changes, nasal permeability may increase, and the nasal air resistance may reduce.[72,74,75] RME has been associated to changes in upper airway dimensions; however, the extent of these changes, the long-term effectiveness and the relationship between airway dimensional changes and breathing capacity is still controversial, especially those changes related to the oropharynx portion.[54,81–84]

Different methods for evaluating the upper airway dimensions and function are available, although each has its advantages and drawbacks.[84] The CBCT allows the rendering of the volume in 3D view, permitting the assessment of airway dimensions, linear and angular measurements. Although it has a higher radiation dose than the cephalometric radiographs, CBCTs are more accurate than 2D images.[85] With the acoustic rhinometry is possible to gather volumetric and cross-sectional area data from reflected signals, however, this method is commonly used by ENTs but not by orthodontists. The PSG gives information on the airway function throughout the AHI.

There are several types of reviews, one of them is the umbrella review used in cases of the evidence of a topic should be compiled from multiple reviews. The umbrella review focuses on highlighting reviews that address interventions and their results for a specific condition.[86] In this sense, since there are numerous published systematic reviews addressing the RME and its associations to the upper airway dimensional changes, we intend to map and summarize the research findings on the upper airway function and dimension. As well as outline the methods used to evaluate the upper airway across the systematic reviews and also to identify potentially complementary approaches on the topic.

2.2 Methods

2.2.1 Protocol and registration

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA – P) was used as a guideline for the methodological approach of this study.[87] In addition, the layout of this study was based on the PRISMA checklist.[88]

2.2.2 Eligibility criteria

Systematic reviews in which RME treatment outcomes in children and adolescents were evaluated in regard to upper airway dimensions or function were included in this umbrella systematic review. Studies that investigated upper airway changes using 3D images (CBCT, CT, MRI), acoustic rhinometry, rhinomanometry, polysomnography correlated to RME were included. Since the focus of this study is RME, studies on expansion using palatal anchorage with miniscrews surgically assisted maxillary expansions were excluded, as well as studies including syndromic patients. No limitation of time or language was imposed.

2.2.3 Information sources

To identify likely compatible papers related to our inclusion criteria, the following databases were searched: Cochrane, EMBASE, Medline, and PubMed. Also, a hand search was carried out. The search was conducted in April 2018, and an update was carried through a year later, in April 2019. The search results were exported to Rayyan Software (Qatar Computing Research Institute, Doha, Qatar)[89] in which the duplicates were excluded. (Figure 2.1)

2.2.4 Search

The final search strategy is displayed in Appendix 1, it shows the search strategy and truncations for each database. Terms used for the search were: airway*, Damon, expan*, hyrax, maxil*, nasal cavity, naso-pharyn*, nasopharyn*, nose, oro-pharyn*, oropharyngeal, palat*, palatal expansion technique, pharyn*, pharynx, rme, rapid maxil* expan*, systematic, review. Those terms were adapted to each database and are included in Appendix 2.1.

2.2.5 Selection of sources of evidence

The studies were evaluated by two reviewers (SGC and KH) independently screening titles and abstracts using a web-based citation management program (RefWorks, ProQuest LLC; and Rayyan, Qatar Computing Research Institute, Doha, Qatar). The articles were screened by full text in the second phase by the same two reviewers, in case of disagreement a third reviewer was consulted (CPP).

2.2.6 Data charting process and Data Items

The data were extracted by the first examiner (SGC) and checked by the second examiner (KH) charted from each article, and the key features were listed: authors, country, year, type of appliance, the area of the airway evaluated, modalities of evaluation (e.g. volume, minimum cross-sectional area, Apnea/Hypopnea Index, Oxygen saturation), type of test to assess airway changes, main results (Table 2.1). In addition, the data included in each systematic review were summarized in Table 2.2.

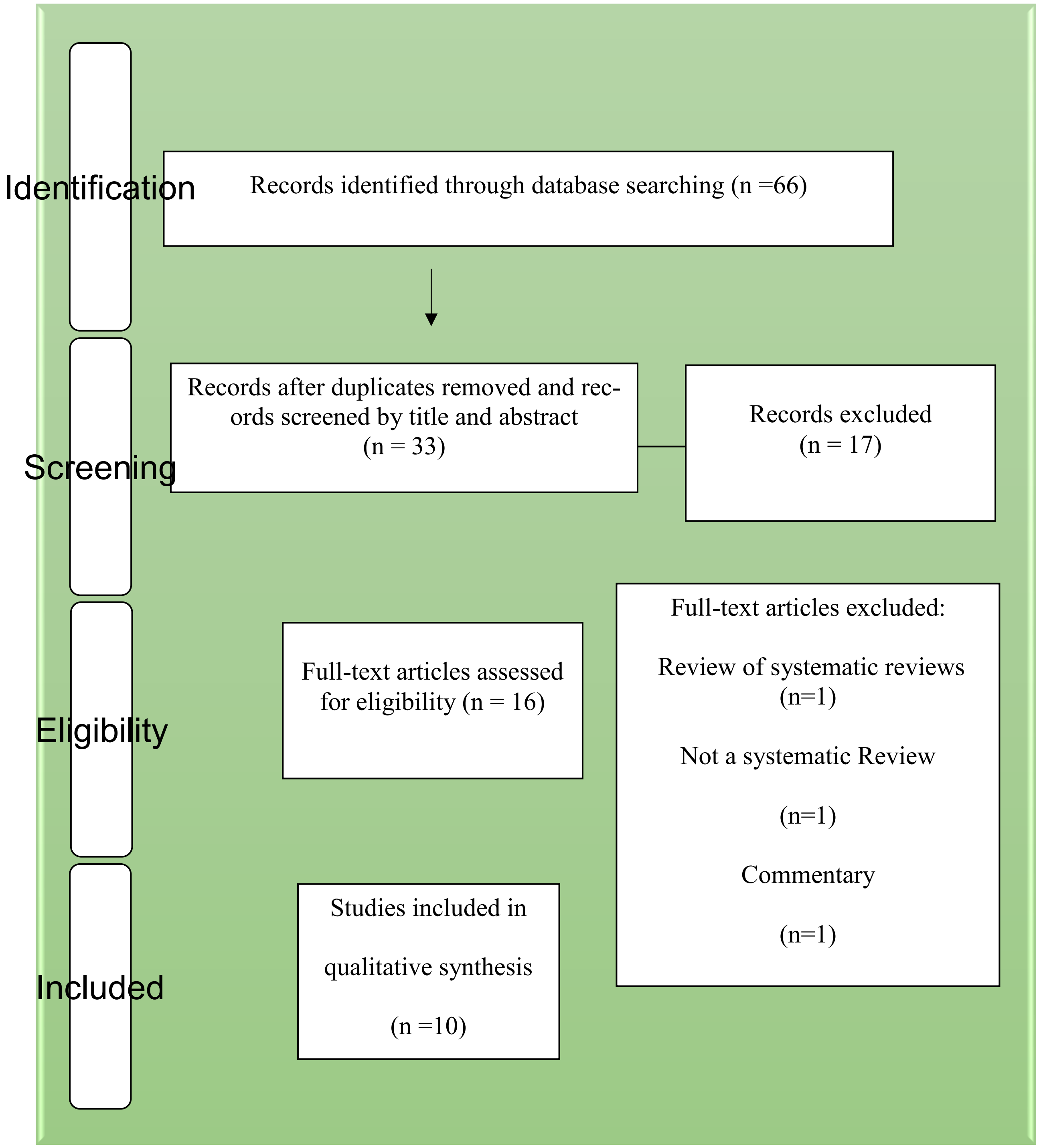


Figure 2.1: Flow chart of literature search

2.2.7 Critical appraisal of individual sources of evidence

The assessment of the methodological quality of each systematic review was executed using the AMSTAR 2 tool. Differently, from the first version of AMSTAR, this tool does not generate an overall score. Instead, the second version focuses on critical and non-critical weaknesses.[90] The high-quality study receives "no or one non-critical weakness; this way, the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the questions of interest."[90] Moderate quality is given to the review that receives "more than one non-critical weakness: the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review".[90] However, multiple non-critical issues may decrease certainty and would be convenient to decrease the quality of the study from moderate to low.[90] Low quality are those having "one critical flaw with or without non-critical weakness: the review has a critical flaw and may not provide an accurate and comprehensive summary of available studies that address the question of interest".[90] And the studies assigned as critically low have "more than one critical flaw with or without weakness" leading to a study that should not be entrusted to have an accurate summary of the included studies.[90]

2.2.8 Summary measures

The studies were evaluated regarding the volume and minimal cross-sectional area changes in the upper airway (nasal cavity, nasopharynx, oropharynx) and respiratory function (AHI). Also, the type of exams (CBCT, AR, nPSG) was assessed, as well as the type of RME and long term effects.

2.2.9 Synthesis of results

The studies where grouped according to the portion of the airway analysed, nasal cavity, nasopharynx, oropharynx, and hypopharynx; and described in terms of percentages or statistics according to each study.

2.2.10 Risk of bias across studies

The risk of bias (RoB) across studies was evaluated comparing the differences across studies such as type of RME, type of exams and type of outcome. Also, a comparison of the RoB among individual reviews was assessed.

2.3 Results

2.3.1 Selection of sources of evidence

A total of 66 studies were found from the databases' search. After managing duplicates 33 studies were assessed based on the title and abstract, where 17 were excluded. The remaining 16 reviews were screened by assessing their full text. The references of the included studies were screened for possible new inclusions. In the end, ten reviews were included in this umbrella review. The complete information regarding studies' selection and inclusion are described in Figure 2.1.

2.3.2 Characteristics of sources of evidence

The characteristics associated with the target group, number of articles included, main findings, databases searched, type of appliance, a portion of airway analysed, type of evaluation and tests or exams used to evaluate upper airway dimensions and function are summarized in Tables 2.1 and 2.2.

2.3.3 Critical appraisal within sources of evidence

The AMSTAR tool results showed Table 2.3 is divided into 16 questions and the results displayed into 4 possible categories; High, Moderate, Low and Critically Low quality of evidence. Only one systematic review was ranked with High quality of evidence[72], one received Moderate ranting[84]; three were rated Low[23,54,91]; and five received a Critically low rating[82,92–95].

The lack of a protocol registered was the most common critical domain across the studies. Although it is not possible to affirm the lack of register or if the information was not reported in the papers.

2.3.4 Results of individual sources of evidence

General information

Lee et al. analysed the pharyngeal changes after RME or protraction, but we focused only on the results related to RME alone.[95] Di Carlo et al. evaluated the upper airway changes comparing CBCT protocols.[91] Vale et al. evaluated the studies available examining patients with OSA treated with RME for posterior cross-bites, analysing the AHI rates after the RME treatment.[93] Ortu et al. evaluated changes in oropharyngeal airway volume and MCA after the use of RME.[94] Camacho et al and Huynh et al evaluated upper airway changes after RME in children diagnosed with OSA.[54,82]

AMSTAR2										
Questions	Alyessary A. et al.	Lee et al 2018	Vale et al. 2017	Di Carlo et al. 2017	Buck LM et al. 2017	Camacho M. et al. 2016	Huynh et al. 2014	Ortu et al. 2014	Baratieri C et al. 2011	Gordon et al. 2009
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	N	N	N	PY	Y	PY	PY	N	PY	PY
3. Did the review authors explain their selection of the study designs for inclusion in the review?	N	N	N	N	Y	N	Y	N	Y	N
4. Did the review authors use a comprehensive literature search strategy?	PY	PY	PY	PY	Y	PY	Y	Y	PY	PY
5. Did the review authors perform study selection in duplicate?	N	Y	Y	Y	Y	Y	Y	Y	Y	Y
6. Did the review authors perform data extraction in duplicate?	N	Y	Y	N	Y	Y	Y	N	Y	N
7. Did the review authors provide a list of excluded studies and justify the exclusions?	N	N	Y	N	Y	N	Y	N	Y	Y
8. Did the review authors describe the included studies in adequate detail?	N	PY	Y	Y	Y	PY	Y	Y	Y	PY
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	N	Y	PY	Y	Y	Y	N	N	Y	Y
10. Did the review authors report on the sources of funding for the studies included in the review?	N	N	N	N	N	N	N	N	N	N
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	NA	Y	Y	NA	Y	Y	Y	NA	NA	NA
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	NA	N	N	NA	Y	Y	N	NA	NA	NA
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	N	N	N	Y	Y	Y	N	N	Y	N
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	N	Y	Y	N	Y	Y	Y	N	N	N
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	NA	N	N	NA	Y	Y	N	NA	NA	NA

16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Y	N	N	Y	Y	Y	Y	Y	Y	N
Result	CL	CL	CL	L	H	L	CL	CL	M	L

Table 2.3: AMSTAR 2 critical appraisal tool for quality assessment

Gordon et al. evaluated nasal dimensional changes through acoustic rhinometry after RME treatment.[23] Buck et al. described the volumetric changes in the upper airway after RME.[72]

Upper Airway function

Camacho et al., Vale et al. and Huynh et al. evaluated the efficacy of RME in pediatric patients diagnosed with OSA.[54,82,93] Their principal findings were a decrease of AHI after RME; improved mean oxygen saturation and lowest oxygen saturation after RME.[54,82,93] Camacho et al. stated that RME could be a primary treatment option for children with small tonsils or the second option in patients who adenotonsillectomy failed and OSA persisted, in children with the constricted maxilla.[54] Nonetheless, according to Camacho et al, the patients with residual OSA after adenotonsillectomy and RME treatment could have considered oropharyngeal sites of collapsibility (epiglottis, supraepiglottis, and tongue base sites).[54] The reduction in the obstruction could be a secondary factor associated with post-RME treatment such as an increase in nasal cavity size and consequently improve in the nasal flow; better tongue position after maxillary width expansion; a stimulus for normal positioning of the mandible after the maxillary teeth repositioning.[54] An immediate overall decrease of 70 % in the AHI was found with a reduction from a mean of 8.9 ± 7/hour (h) to 2.7 ± 3.3/h after the treatment with RME; aside from two studies, the other 15 showed at least 50% reduction in AHI after the RME.[54] According to Vale et al. the mean decrease rate for

AHI was 3.24 at a 95% confidence interval (CI) [0.34-6015].[93] A more significant reduction on the AHI levels was seen in children with small tonsils or no tonsils.[54] Regarding oxygen saturation, studies reported an improvement between 0.4% to 5.7% in the mean oxygen saturation and a 9% improvement of lowest oxygen saturation.[54] Nasal flow increase was also reported ($p<0.05$).[84] Although all the results mentioned above, one author stated that it is possible that part of the results is related to growth and spontaneous remission of OSA.[54] Huynh et al. reported a high heterogeneity (I^2=98.4%, $p<0.001$) as well as Vale et al. (I^2= 98.02%, $p<0.0001$ for AHI improvement, and I^2=95.53% $P<0.0001$ for AHI normalization).[93] According to them, likely due to the fact that there were just a few studies included and they were from a few research author groups.[93] Although RME can influence positively in the breathing capacity of patients with OSA, RME treatment is an auxiliary method[93] and should be used only when orthodontically indicated[8].

Upper airway dimensional changes

Alyessary et al. showed that most of the results pointed for an increase in the anterior nasal cavity area, from pre to post-treatment (11.7%), post-expansion to post-retention (22.2%) and pre-expansion to post-retention (35.7%).[92] Similar results were found in the middle and posterior nasal cavity areas (10% and 15% respectively).[92] Nasal width increase was found in several studies, its volume was reported to have increasing dimensions after RME treatment.[67,79,91]There was also an increase in the nasal volume reported (11.3%).[92] Lee et al. reported changes in the nasal passage airway volume ($p=0.004$).[95] However, no changes were seen in the lower airway and the airway below the palatal plane ($p>0.05$) in the same study.[95] Gordon et al results showed an increase in the nasal volume and minimal cross-sectional area (MCA); one study demonstrated MCA increase after RME in two groups, one before the pubertal growing peak and the other after the pubertal growing peak.[23] However, a higher decrease in the MCA saw after the retention phase in the group after the pubertal growing peak.[23] Overall Buck et al found the total airway volume increased; when evaluated via AR studies showed a statistically significant increase in nasal volume ($p<0.001$) with 2 mm^3 to 6 mm^3 increase.[72] They found an increase in the velopharynx, nasopharynx, oropharynx and hypopharynx volumes; however, there was a decrease in the remaining volume gain after the retention when compared to the volume results right after the expansion in the nasopharynx and oropharynx.[72] Regarding oropharynx, one study found differences in oropharyngeal volume, however those changes were not statistically significant, but another study showed a statistically significant increase in oropharyngeal volume after RME.[62,79] Conversely, one study showed a decrease in the oropharyngeal volume although not statistically significant,[67,91] and other three studies found no differences in the oropharyngeal volume.[60,61,76,91] Out of five studies analysed by Ortu et al., two did not find changes in the oropharynx volume after RME; the other three found increases, one in the retropalatal cross-sectional area, one in the retropalatal plane, and one in oropharyngeal volume.[94] One author stated that the improvement of airway ventilation was related to the "new" lower position of the tongue.[76,91] The reduction of upper airway resistance was linked to the changes in the nasal valves, the widening of the nasopharyngeal cavity, and the increase in the total airway volume.[92] Baratieri et al. noted through their study a moderate level of evidence showing that RME increases nasal cavity width and posterior nasal airway was found according to the quality of evidence tool assessed.[84]

Long-term effects

An overall decrease in AHI results after RME treatment was described by Huynh ($p=0.005$ from baseline to follow up of 6-12 months in one study, and $p=0.046$ from baseline to follow up at

10-16 months in another study).[82] Baratieri et al. evaluated the long-term effects of RME on upper airway dimensions.[84] They stated an indication of the stability of the results for at least 11 months after the treatment with RME, although one study concluded that there was stability up to five years.[84]

Type of RME

Hyrax,[84,91] Haas,[84,91] were used in the studies included in each systematic review. Some studies also reported as banded[91] or bonded[84,91]. The most common reported activation protocol was two turns a day.[84] However, some authors described poorly the type of appliance. Huynh's description of studies was limited; there was no information on the type of appliances used, only vague descriptions such as "fixed", or "in situ" or "ex-situ".[82] All the articles evaluated by Vale et al reported the use of banded RME appliances.[93] Alyessary et al., Lee et al., Ortu et al and Camacho et al. did not mention the type of RME used in the included articles.[54,92,94,95]

Type of exams

The reported exams used to appraise the breathing capacity were Polysomnography, Acoustic Rhinometry (AR),[84,92,96]and Rhinomanometry.[84,92] The upper airway dimensional changes where assessed with either CBCT,[84,91,92,94,95] CT,[72,92] or MRI.[92]

2.3.5 Synthesis of results

Ten systematic reviews were included in this study, all of them were written in English and published between 2009 and 2019, although no restrictions to language nor year were considered as inclusion/exclusion criteria. One study was from the United States, Portugal, and Italy[54]; one from Malaysia and Singapore[92]; one from Brazil[84]; two from Canada[82,96]; one from Taiwan[95]; one from Portugal[93]; one from a group from Australia, Germany, and Greece[72]; and two from Italy[91,94]. Out of the ten systematic reviews, three studies focused on patients with OSA, for the others OSA was not an inclusion criterion.[54,82,93] The reviews were critically appraised for quality of evidence using the AMSTAR 2 tool[90]; the results showed only one[72] systematic review scored High quality of evidence. From the included systematic reviews, it was possible to retrieve 53 articles in total that studied upper airway changes after orthodontic treatment using RME in patients with a constricted maxilla (bilateral or unilateral cross-bites). In total, 53 studies included evaluated different areas of the upper airway, 19 of them reported results related to breathing capacity, two related to the oral cavity or the palatal volume, 29 related to the nasal volume, 11 related to the nasopharynx and 9 related to the oropharynx The mean age of the accessed patients was from 5.9 to 14 years old. The overall conclusion that can be reached is that an increase in the nasal cavity volume, a decrease in airway resistance and decrease in AHI are usually observed after the treatment with RME. Nasopharyngeal volume and minimal cross-sectional area increases were shown with seven articles claiming an increase after RME and three claiming no change appeared. The major uncertainty on the results was left to the oropharynx where three studies reported an increase in the oropharynx, four reported no changes and two reported a decrease in oropharynx after RME treatment.[61,62,67,76–79,97,98]

The most common appliance used for RME amongst the 53 articles included in the systematic reviews analysed in this study was the Hyrax.[72,84,91] However, besides Baratieri, Gordon, Buck and Di Carlo that described all the types of appliances used under the nomenclature RME, the other studies only labeled RME or bonded or banded RME.[23,54,72,84,91]

Alyessary et al. complained about the lack of information regarding relapses across the studies analysed; conversely, Camacho et al. highlighted one study in which the results showed relapses after 6.5 years related to AHI and skeletal changes associated with narrow palate and overjet.[54,92] Also, Baratieri reported findings on the long-term effects of RME on the upper airway, showing at least 11 months of stability; although one study described up to 5 years stability.[84]

Risk of bias across studies

A large number of dissimilarities were seen across the studies. The studies differ in regards to the portion of the airway analysed, which could be interesting to have results focused in just one area.[94] On the other hand, the boundaries delimited across the included studies in each review for times were different. The retropalatal plane described in one study was at the same anatomic boundary as the nasopharyngeal space of another included study and was the same boundary of the oropharyngeal space in another. This discrepancy leads to uncertainties among the results.

In addition, the differences in types of exams turn the comparator factor impossible; it is not possible to compare the dimensional changes found through AR to those found in CBCT. The lack of more studies evaluating the long effects of RME on upper airway still leads to skepticism.

The main RoB problem within studies was the lack of a registered protocol, sometimes the authors mentioned there was a protocol, however, there was no registration number. Only two studies reported a previous plan for the meta-analysis and investigation of the heterogeneity causes.[54,72] Four studies did not describe in detail the studies included.[23,54,92,95]

2.4 Discussion

2.4.1 Summary of evidence

The objective of this umbrella review was to summarize the findings on the effect of the RME on the upper airway. Methodological flaws and differences do not support the comparison between some results, moreover, can lead to inaccuracies; especially concerning the boundaries and nomenclatures nasopharynx, oropharynx, and retropalatal pharynx.

The finding on the increase of nasal cavity volume after RME treatment seems to be consistent and reported by several articles.[23,72,82,84,91,92] Overall the results showed an increase in the nasal cavity of 5cc or 10-12%.[72,91,95,99] Supporting articles associated these volumetric changes to decreases of nasal resistance and normalisation of AHI,[54,82,93] showing reduction on AHI the results ranging from a decrease of 8% to 95%[54,91,93,96]. However, caution is needed because is it not possible to automatically imply breathing function improvement only by AHI. In regards to nasopharynx dimensional changes, several studies have found increases in volume and/or MCA, demonstrating increases of up to 29%.[70,72,77,91,97,100] On the other hand, fewer studies have evaluated the effects of RME in the oropharynx and the results are controversial: three studies reported an increase (retropalatal plane; retropalatal airway and oropharyngeal sagittal and axial area), four studies reported no changes and two studies reported decreases of oropharynx dimensions.[61,62,67,76–79,97,98]

In general, the heterogeneity was found high[91,93,95], although not all the systematic reviews have performed the meta-analysis. The systematic reviews that evaluated upper airway dimension were rated with a high level of evidence;[72] moderate level of evidence[84], low level of evidence[23,91] and critically low level of evidence[92,94,95]. The reviews that analysed AHI were scored with critically low[82,93] and low[54]quality of evidence. Although the review of Huynh et al was fully organized and complete, they did not report and discuss the risk of bias individually, for this reason, according to AMSTAR 2 tool their rating dropped off to the critically low quality of evidence.[82]

An increase in the palatal volume may be related to a better repositioning of the tongue posture, increasing the airway space in the oropharynx level.[72,101] The tongue might be positioned closer to the roof of the palate, displacing the tongue away from the oropharynx, possibly leading to a more consistent nasal breathing.[81] However, caution is needed to correlate findings in this sense because the difference in tongue position can be related to swallowing or breathing phases during the CBCT exams when children are being imaged; even when the radiograph technician uses a strict protocol, tongue movement is not unlikely to occur.[91]

The transverse changes in the maxillary halves and consequently on the nasal walls after the maxillary expansion procedure seems to be directly related to the nasal cavity dimensional changes.[72–75] Furthermore, these changes might be related to the findings on reduced nasal resistance and normalization of AHI.[81] Based on linear measurements, Lagravere et al. reported in a systematic review that the transverse maxillary statistically significant changes were nasal cavity width (intercondylar width) and inter-alveolar width.[102] Concerning vertical changes, the statistically relevant were changes in the mandibular plane with respect to the palatal plane and SN plane were relatively minor (1.65 and 1.97 degrees respectively).[102] However, some studies have found no significant changes in the transversal skeletal width, although they found changes in the transversal molar and pre-molar width, suggesting dental tipping.[102] While others have supported significant transversal findings, important increases to the maxillary alveolar width were found, but the clinical significance is still questionable.[102] Non-significant anteroposterior skeletal changes were found ($p>0.05$), but significant ($p<0.05$) vertical changes were confirmed in the mandibular plane angulation, however, those findings may not be clinically significant.[84,102]

Regarding the examination types, the polysomnography exam gives a reliable and objective finding concerning the nocturnal breathing capacity. However, since RME anatomical changes might occur in different upper airway levels, it is impossible to know to which part of the upper airway the changes are related to. The AR is an interesting exam that gives cross-sectional area and volume of the nasal cavity and pharynx through the reflection of sound waves. Nasal decongestants can be used to remove pathological constriction effects and acute inflammation.[23] But it is also not possible to know which part of the upper airway has increased in regards to RME effect. Both polysomnography and AR need special equipment and the analysis by an ENT. The CBCT gives an objective measure related to volume and MCA area that is easily comparable to different time-points measurements in case of rigorously repetitive scanning conditions; however, different protocols of head position, threshold, and type of software to analyse the data may result in conflicting results. Additionally, CBCT's have limitations regarding soft tissue analyses.

Few studies evaluated long-term effects of RME on upper airway dimensions; one of them implied higher stability on a group of adolescents if RME was done before the pubertal peak of growth.[23] The higher stability in the group treated before the peak of growth could be related to less palatal suture calcification at the time of expansion and a lower resistance against the expansion forces.[81] In agreement with stability results, Pirelli et al found the RME results to be stable after 12 years in a group of children diagnosed with OSA.[103] Additionally, the long-term effect is not an easy matter of debate considering the Scammon growing curve and craniofacial growing, the different ages are going to address the long-term effects differently.

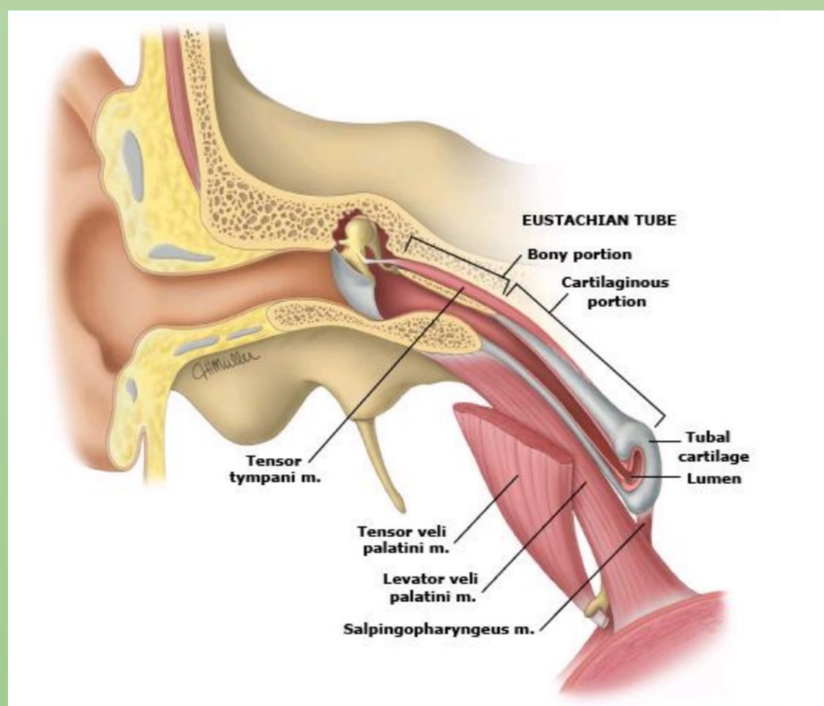


Figure 2.2: Anatomy of the Eustachian tube from https://wd.vghtpe.gov.tw/ent/files/002.pdf and http://www.uptodate.com/contents/image?imagekey=PC/70595&topickey=PC%2F14608&source=outline_link&search=patulous+eustachian+utdPopup=true

During craniofacial growth, the nasopharynx volume can reach rates of up to 80% of increase.[6] Hence, not only the orthodontic treatment can influence the size, but Scammon curve related lymphoid tissue growth will influence the relative upper airway dimensions at the oro- and nasopharyngeal levels as well.[9] The lymphoid (tonsils and adenoids) masses increase fast during the early ages, with a slower development after that, a peak before adolescence and a decrease to adulthood (Fig 2.2).[6,9] Therefore it is possible that the increase in the nasopharyngeal airway is related to the spontaneous reduction of the lymphoid tissue due to age or normal craniofacial growth changes.

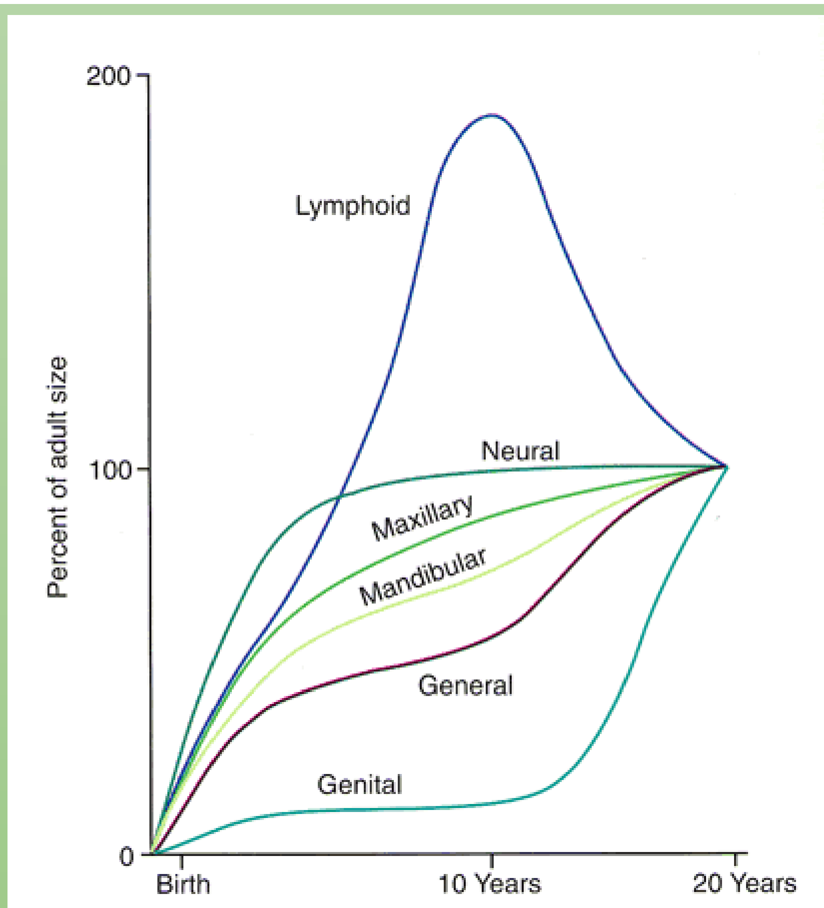


Figure 2.3: Scammon curve

On the contrary of a previous systematic review of systematic reviews on the same RME treatment and its effects on upper airway subject, we decided to include studies that focused on sleep-breathing disorders' patients and also those that were done in healthy patients.[81] Due to the fact that we intended to summarise the finding around this area, and since those patients underwent to RME treatment, the results on pharyngeal and nasal dimensions, breathing capacity, AHI, and oxygen patency are extremely valid to be analysed. Since 2D imaging exams have been related to the superimposition of structures, magnification and low accuracy to visualise upper airway, we decided not to include studies based on lateral 2D cephalometric radiographs.[15–17]

Camacho et al. reported the Body Mass Index (BMI) of the population sample of the included studies; however, besides the number itself of the mean BMI, no comments were made in regards of BMI.[54] Martinelli et al reported a high prevalence of OSA in a group of obese children, however, no correlation was found between BMI and the presence of OSA.[104]

Limitation

The authors of this umbrella review acknowledge that one included study[94] was not a systematic review, but a review. In these terms, that review missed information and methodological format commonly used in systematic reviews. Although the decision to include this study was based on the fact that it is a good review of the topic proposed by this umbrella review.

2.5 Conclusion

A massive amount of research has been published linking RME changes to an increase in the nasal respiratory capability, nasal volume and linear transverse enlargement.[55,60–62,67,82,84] However, inconsistencies and disagreements between the included studies' results especially on the oropharyngeal dimensional changes after RME, led to uncertainties about the real effect of RME on the oropharynx region. In line with our proposal for this systematic review, more studies with improved methods on the oropharyngeal changes related to RME are necessary to try to understand the real effects of RME in the cited region of the pharynx. Although, according to some authors, RME can influence positively in the breathing capacity of patients with OSA[54,82,93], RME treatment is an auxiliary method[93] and should be used only when orthodontically indicated.

Authors Year	*Mean age BMI (if reported)*	*Effects of RME on airway*
Monini et al. 2009	7.8 y	There was an improvement of nasal respiration in children via a widening effect on the nasopharyngeal cavity.
Aloufi et al. 2012	14.2 y	Positive effect on the upper pharyngeal airway. RME did not significantly improve the mode of breathing.
Iwasaki et al. 2012	NR	Improvement of nasal airway ventilation by rapid maxil-lary the expansion was detected by computational fluid dynamics
Iwasaki et al. 2014	NR	The nasal airway ventilation conditions were improved and constriction of the pharyngeal airway less likely after RME
Caprioglio et al. 2014	NR	Increases in total airway volume
Fastuca et al. 2015	8.9 y	The upper, middle, and lower airway volumes, and oxy-gen saturation significant increased. 71% of AHI decrease
Izuka et al. 2015	NR	Significant gain in airway the volume of the nasopharynx and nasal cavity, and also in the anterior and posterior widths of the nasal floor
Compadretti et al. 2006	9.5 y	Increase in nasal width. Decreased nasal airway resistance and increased total minimal cross-sectional area using AR
Enoki et al. 2006	NR	Decreased nasal airway resistance but no a a significant change in minimal cross-sectional-area
Doruk et al. 2007	13 y	Increased nasal cavity volume evaluated with CT and AR
Palaisa et al. 2007	11.5 y	10% increase in the nasal area and nasal volume using CT

Oliveira et al. 2008	13 y	A mean reduction of nasal airway resistance; and mean increases in total nasal volume analysed via AR without decongestant and model scanning and nasal valve area
Haralambidis et al. 2009	14.5 y	A significant average increase of 11.3% in nasal volume. Sex, growth and the skeletal relationship did not influence measurements
Matsumoto et al. 2010	NR	RME significantly increased nasal and maxillary width, but the nasal mucosal effects were subtler and not stable
Görgülü et al. 2011	13.8 y	12.1% increase was measured in nasal cavity volume evaluated through CT
Langer et al. 2011	NR	RME does not influence on the nasopharyngeal area or nasal airway resistance in long-term evaluation
Cordasco et al. 2012	9.7 y	Significant enlarge the dimension of the nasal cavity, and the increment is larger in the lower part of the nose and equally distributed between the anterior and the posterior part of the nasal cavity.
Smith et al. 2012	12.3 y	Significant increases in nasal cavity volume and naso-pharynx volume. No increase found in the oropharynx, hypopharynx, and maxillary sinuses. CT was used to evaluate the airway
Itikawa et al. 2012	NR	No effect on nasal resistance since the nasal bony expansion is followed by a mucosal compensation
Chang et al. 2013	12.9 y	No changes in retropalatal and retroglossal and total volumes. Only the cross-sectional area of the upper airway at the posterior nasal spine to basion level significantly showed a moderate increase after RME
Pirelli et al. 2015	8.6 y BMI 22.7 ± 1.3	95% AHI decrease, 16% improvement in LSAT
Taddei et al. 2015	8.9 y	7.7% AHI Decrease
Villa et al. 2015	6.2 y BMI 19.9 ± 2.2	51% Decrease in AHI
Hosselet et al. 2010	12 y	55%AHI decrease
Villa et al. 2014	6.6 y BMI 18.8 ± 3.4	52% AHI Decrease
Miano et al. 2009	6.4 y BMI 18 ± 3.5	69% AHI decrease
Villa et al. 2007	6.9 y BMI 16.7 ± 3.6	74% AHI decrease
Marino et al. 2012	5.9 y	24% AHI Decrease
Pirelli et al. 2012	7 y BMI <24	55% AHI Decrease, 11% LSAT improvement
Villa et al. 2011	6.6 y BMI 16.7 ± 3.6	63% AHI Decrease, 2% LSAT improvement

Pirelli et al. 2010	7.3 y BMI<24	95% AHI decrease
Cameron et al. 2002	11.8 y	Increase in nasal width.
Baccetti et al. 2001	12 y	Increase in nasal cavity width.
Zhao et al. 2010	12.8 y	Retropalatal differences found in oropharyngeal volume when comparing subjects with narrowed maxilla with subjects without narrowed maxilla
Christie et al. 2010	9.9 y	Increases on nasal width
Zeng and Gao 2013	12.7 y	Statistically significant nasal cavity width and volume increase, and Oropharyngeal decrease using CBCT
Ribeiro et al. 2012	7.5 y	Nasal cavity increase and increase in oropharyngeal median sagittal area (p=0.01) and lower axial area (p=0.04) after RME. No change in nasopharynx volume.
Pangrazio-Kulbersh et al. 2012	13 y	Increase in the nasal cavity, and sinus volume, but no change in posterior airway volume using CBCT
Baratieri et al. 2014	9 y	Increase in nasal cavity width.
Pirelli et al. 2004	8.6 y	Changes in AHI, Arterial oxygen saturation; sleep quality
Guilleminault et al. 2011	6.5 y	Changes in AHI, Arterial oxygen saturation; Respiratory disturbance index
Almuzian et al. 2018	12.6 y "normal" BMI	Statistically significant increase in nasopharynx volume and retropalatal oropharynx using CBCT
Azaredo 2014	10.7 y	No statistically significant changes in total airway volume
Babacan et al. 2006	12.3 y	Statistically significant increase in the nasal cavity volume of about 12.5% evaluated through AR without decongestant
Cappelletti et al. 2008	9 y	Statistically significant increase in nasal cavity evaluated through AR with a decongestant
Darsey et al. 2012	13.8 y	No changes in the maxillary sinuses
Kabalan et al. 2015	14 y	No significant changes in the nasal cavity after RME evaluated with AR
Li et al. 2015	12.1 y	29.9% Increase in the nasopharyngeal volume evaluated with CBCT. No changes found in the oropharynx
Manini et al. 2007	7.5 y	Increase in the palatal volume evaluated with Photogrammetry
Sokucu et al. 2010	12.4 y	Increase in nasal cavity volume evaluated with AR with and without decongestant
Bicakci et al. 2005	12.5 y	Increase in the nasal minimal cross-sectional area. However, a decrease was seen after the retention phase

Iwasaki et al. 2013	9.82 y	Decreased intra oral airway volume, and increase the pharyngeal volume
El et al. 2014	14 y	No significant change in oropharyngeal volume.
NR- Not reported		

Table 2.2: Studies included in the systematic reviews

Chapter 3: Oropharyngeal dimensional changes following maxillary expansion: the methodology and reliability

3.1 - Introduction

As seen in chapter two, a great amount of research has been linking the RME to an increase in nasal respiratory capability, nasal volume, and linear transverse enlargement.[55,67,84] However, inconsistencies and disagreements between studies' results on oropharyngeal volumetric and cross-sectional area dimensional alterations after RME lead to uncertainties about the real effect of RME on the oropharynx region. Moreover, the type of assessment used to evaluate the upper airway volume is essential to imply reliability to the results. When comparing the upper airway structures analysed via 2D and 3D image exams, the CBCTs show more accurate results due to the addition of mediolateral information of the oropharyngeal airway .[8,105–107] CBCTs are somehow effective to assess the upper airway and surrounding anatomic structures and to evaluate and monitor upper airway changes after orthodontic treatments.[8] The assessment of upper airway through CT or MRI is possible and trustworthy; however, their higher costs, higher radiation dose (CT) and restricted access limit their use.[16] CBCT, when compared to MRI and CT, has lower cost, relatively less ionizing radiation than CT, and is easily available for the dentist.[40,108] CBCT's accuracy and reliability have been studied and validated in several previous studies.[34,35,39,108–110] 3D images generated from CBCT reconstructions have been used to assess different craniofacial problems enabling hard and soft tissue diagnostic and morphometric analysis.[5,8,111–113]

To build the 3D model, a software is required to convert the DICOM files into 3D images.[16] The process of converting raw CBCT data into a 3D imaging its called reconstruction. The software may use different types of craniofacial segmentation using CBCTs data: manual and automatic/semi-automatic. The manual segmentation is more accurate, but also more time consuming due to the necessity to, slice by slice, delimitate the area to be included.[39–41] On the other hand, in the automatic/semiautomatic method, the software automatically differentiates the air from neighboring structures according to the grey values determined as the threshold.[39] Two greatly used software for segmentation among orthodontists are Invivo (Anatomage, San Jose, California, US) and Dolphin (Dolphin Imaging & Management Solutions, Chatsworth, California US), both automatic software considered semi-automatic tools to assess upper airway segmentation.[39,40]

The accuracy validates a 3D analysis.[16] Nevertheless, reliability appraisal is also important to analyze the measurement agreement and consistency of observers in a tested method,[114] and to determine the reproducibility of the methodology[16]. To establish a high-quality methodology, inter-examiner and intra-examiner reliability tests were performed. The research questions for this part of the study are:

- Are the examiners reliable to evaluate oropharyngeal minimal cross-sectional area and volume using the Invivo and Dolphin software?
- Are there differences in the oropharyngeal measurements between the Invivo and Dolphin software?

3.2 - Methods

This project derived from an original study approved by the Health Research Ethics Board, University of Alberta number Pro00013379.

Using Walter et al recommendations for the sample size calculation and optimal parameters for reliability studies,[114] the following parameters were used: α=0.05, β=0.2 (implying a power test of 80%), n=3 (number of replicates – number of repetitions), p_0=0.7 (minimum acceptable level of reliability) and p_1=0.9 (expected level of reliability). For those parameters, the sample size required was 12 subjects. Having stated that, for the methodology and reliability appraisal, the data consisted of 24 patients with unilateral or bilateral posterior cross-bites, 12 patients treated with Hyrax and 12 patients treated with Damon in the orthodontic clinic at the University of Alberta, Edmonton Canada. The inclusion criteria were scans from 11 to 17 years old patients.

CBCTs were taken with the I-CAT New Generation machine (Imaging Sciences International, Hatfield, PA, USA) at 120 kVp, 7 mA and 8.9 seconds, 0.3 voxel size and 16 x 13 cm field of view (FOV). Patients underwent imaging evaluation at 3 time-points: T1- before treatment, to receive evaluation and diagnosis on dental and craniofacial orthodontic discrepancies; T2- right after the maxillary expansion achieved (6 months from the start of treatment); and T3- after completion of treatment. All images were taken by one of the two radiology technicians, at the Radiologic clinic of University of Alberta following a standardized protocol for this study. The patients were instructed to stay still with natural head position, Frankfort Plane parallels to the horizontal plane, the patients' head was stabilized with a strip to standardize the head and neck position and to prevent movements. The patients were instructed to maintain the tongue right behind the upper central incisors and in maximum intercuspation. The images were stored as DICOM files and made anonymous for blinding purposes. The CBCT data was assessed through Invivo Software version 6.0 (Anatomage, San Jose, California, US) and Dolphin Software version 11.95 (Dolphin Imaging

& Management Solutions, Chatsworth, California US). All imaging was taken for reasons not related to this specific study.

3.2.1 Head orientation previous to measurement

To ensure the same position of images, thus minimizing errors while limiting the landmarks and calculating the volume and the minimal cross-sectional area, a standardized protocol was used to reposition the reconstructed DICOMs according to the head position as follows (figure 3.1):

1-Frontal view: horizontal plane - right and left orbitale cephalometric landmark parallel to the horizontal plane;[115] perpendicular plane - line crossing the projection of anterior nasal spine and pogonion.

2-Lateral view: the Frankfurt plane (porion to orbitale) parallel to the horizontal plane[115].

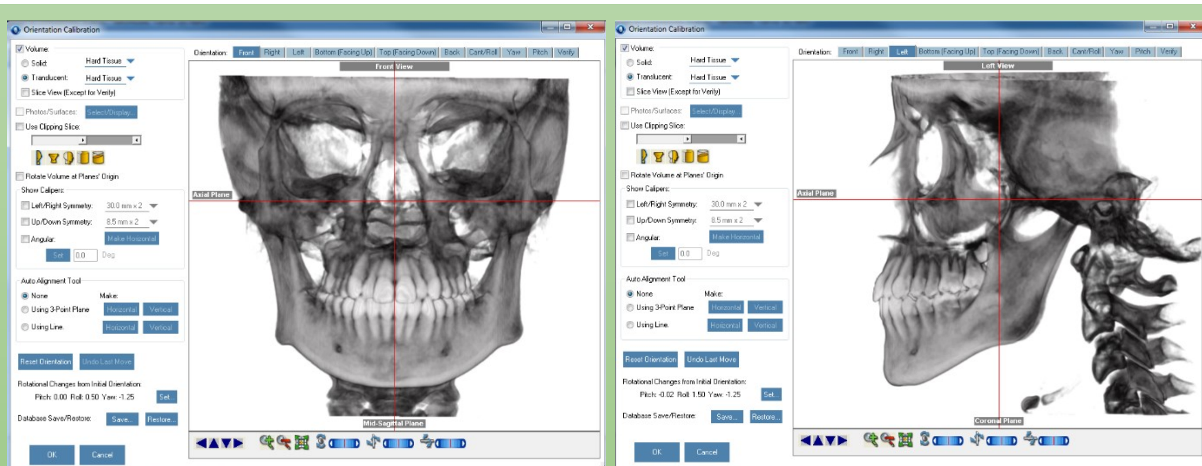


Figure 3.1: Head orientation previous to measurements

3.2.2 The measurements

A calibration protocol between examiners (S.G-C and F.A) consisted of a demonstration of the measurements to be made using Dolphin and Invivo Software. The protocol using Dolphin was to select the boundaries as described in Table 3.1, populate the selected area with “seed points”. Thereafter, the area was automatically filled out in pink by the software giving the volume in cc. The MCA tool was then enabled to permit the software to calculate it; two limiting lines were offered by the software to be placed in the desired area, then the software automatically produces the yellow cut representing the minimal cross-sectional area in mm^2. To evaluate the oropharyngeal volume and MCA using Invivo, the software requires the examiner to place arrows along the desired area and when clicking the end of the last arrow would permit the software to understand the lower limit. However, the delimitation by the software using solely this tool is not accurate to map the exact area desired. To correct the boundaries, double-clicking inside the first automated selected area, lines on the top and bottom borders of the pharynx appears so the examiner can refine the boundaries. Then the Invivo software gives the volume and minimal cross-sectional area values in mm^3 and mm^2 respectively. To allow the comparison with Dolphin the volume values were converted to cc.

After calibration, the examiners did the measurements independently. The measures made were oropharyngeal volume and MCA. Patients’ data were anonymized by the radiologic technician to avoid bias.

The slice in the mid-palatal plane was chosen to insert the boundaries of the landmark (Table 3.1 and Figure 3.2) to allow the software to evaluate the airway using the sinus/airway tool Figure 3.3 and 3.4.

Figure 3.2: Landmarks and oropharynx delimitation: Basion, Posterior Nasal Spine, Cv3, and Hyoid

	Anterior boundary	Posterior boundary	Superior boundary	Inferior boundary
Oropharynx	Line extending from the posterior nasal spine (PNS) to the tip of the hyoid bone	Line extending from the Basion to the inferior border of cervical vertebrae (CV3)	Line extending from the posterior nasal spine (PNS)to the Basion	Line extending from the inferior border of cervical vertebrae (CV3) to the superior/posterior tip of the hyoid bone

Table 3.1: Oropharynx Boundaries[116]

Measurements of oropharyngeal volume and minimal cross-sectional area (MCA) in patients' CBCTs were made three times: at the initial records (T1), 6 months (T2) and at debonding/end of treatment (T3). Inter and intra reliability was assessed using the Intraclass Correlation Coefficient (ICC). The ICC was performed using 12 patients of each group (Damon and Hyrax), a total of 24 patients. To assess intra-reliability, each measurement (T1, T2, and T3) in each patient (n=24) was executed 3 times, with a washout period of a week, by the first examiner (S G-C), and twice with a week apart by the second examiner (FA), specialized in radiology. To assess inter-reliability the results from the first and second examiners were analyzed, also using ICC. ICC values were estimated using a 2-way mixed-effects model.

The results were ranked according to Portney and Watkins' ICC guidelines.[117] The ICC value was considered good between 0.76 and 0.9 and excellent above 0.9.[117] Values under 0.75 were considered inadequate and the need for a second calibration repetition was considered. All the statistical analysis was set at a 5% significance level (95% CI) using the Statistical Package for the Social Sciences SPSS - 25 version (IBM, SPSS Inc, Chicago, IL).

The measurement error analysis (average of the absolute mean differences) was executed to complete the reliability analysis for this study.

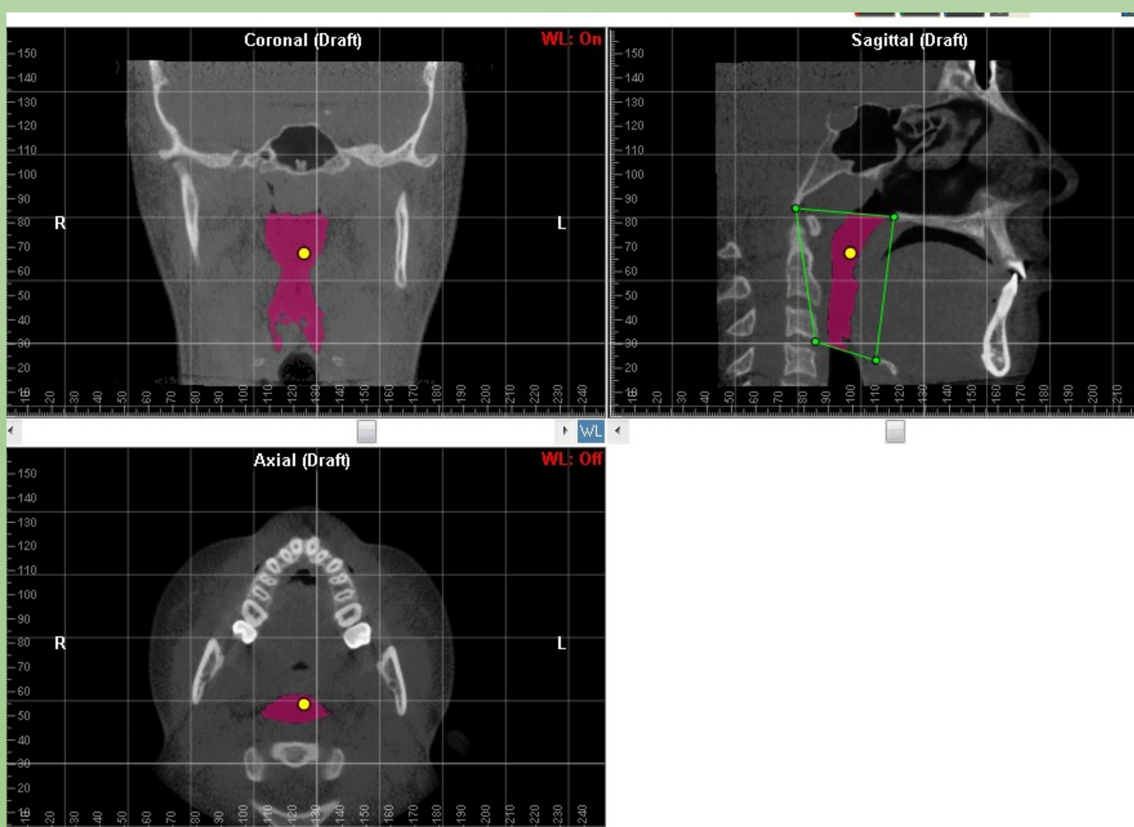


Figure 3.3: Oropharyngeal volume selected - Dolphin

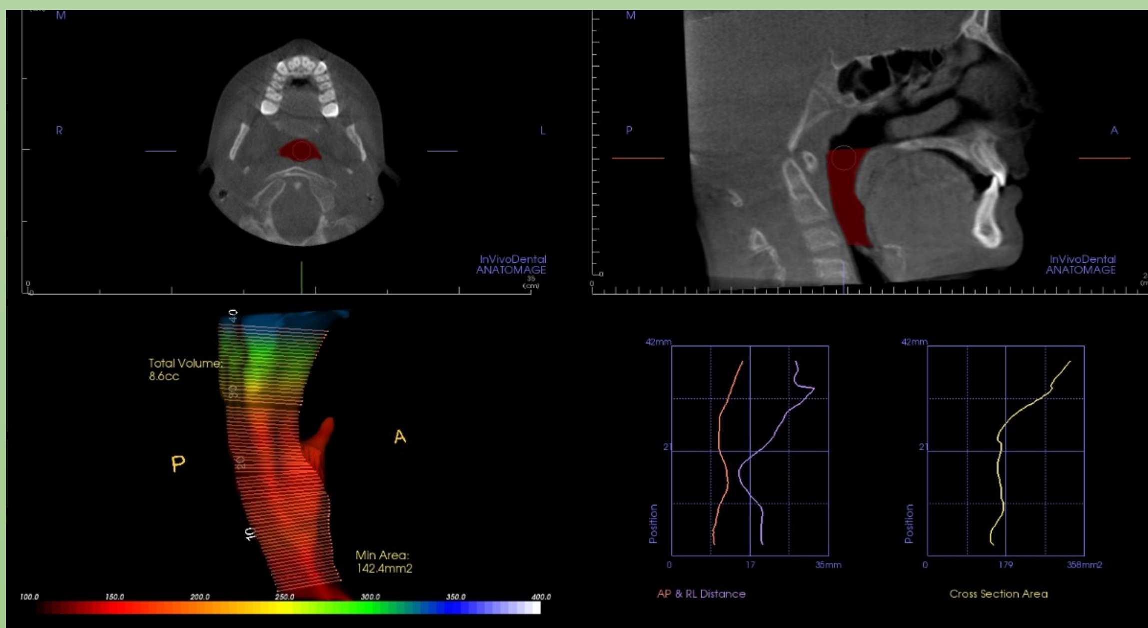


Figure 3.4: Oropharyngeal volume selected –Invivo

While evaluating Invivo and Dolphin software, to determine whether the main effects and interaction effect are statistically significant, an overall test was performed as the first step. If the overall test shows any significance ($p<0.05$), a parametric or non-parametric test should be applied according to the analysis of the assumptions. All the statistical analysis was made at a 5% significance level (95% CI) using IBM SPSS statistics 25 version (SPSS Inc, Chicago, IL).

3.3 - Results

A total of 392 measures were made from examiner 1 and 288 measures from examiner 2 for the reliability test ICC. The first examiner repeated three times the measurement and the second examiner repeated twice. The following measurements were taken into consideration to perform the ICC and the individual results are described in Table 3.2: Invivo volume and MCA, in three time-points, and in two different appliances; three repetitions for the first examiner and two repetitions for the second examiner. The same procedure was done for the Dolphin measures

Since the examiner 1 was reliable, the measurement error results were calculated only for the examiner 1 (described in Table 3.3).

Evaluating Invivo and Dolphin, before the overall test, the model assumptions were evaluated. According to the box plots, the groups are approximately normally distributed (Figure 3.5).

It is possible to confirm that the independence of observations is met, which means that the observations are not influenced by each other. On the homogeneity of variances for each combination of the groups of the three independent variables, the sphericity was not violated. For the factor

Time, the Mauchly test showed a p=0.932 when evaluated with Invivo software, and p=0.685 when evaluated with Dolphin Software. The Overall ANOVA was applied; since the sphericity assumption was met, the “line” sphericity was analyzed. The p-value presented for the MCA= 0.001 and for volume p<0.001(Table 3.4). Since at least one factor showed significance, the next step was analysed to answer the third hypothesis.

	VOL INVIVO TOTAL	95% CI	VOL DOLPHIN TOTAL	95%CI	MCA* INVIVO TOTAL	95%CI	MCA* DOLPHIN TOTAL	95%CI
INTRA EXAMINER 1	0.968	0.945, 0.984	0.948	0.908, 0.975	0.935	0.888, 0.968	0.934	0.882, 0.968
INTRA EXAMINER 2	0.948	0.908, 0.975	0.955	0.921, 0.978	0.955	0.919, 0.978	0.94	0.893, 0.971
INTER Examiners	0.98	0.967, 0.990	0.977	0.960, 0.988	0.971	0.951, 0.985	0.903	0.833, 0.953

Table 3.2: Reliability in volume and MCA measurements using Invivo and Dolphin Software. *Minimal Cross-sectional area

	Vol Invivo	Vol Dolphin	MCA* Invivo	MCA* Dolphin
% M.E.	5.02%	11.89%	14.83%	4.30%
M.E.	0.05 cc	0.12 cc	0.15 mm^2	0.04 mm^2

Table 3.3: Measurement error for examiner 1. *MCA=Minimal Cross-sectional area

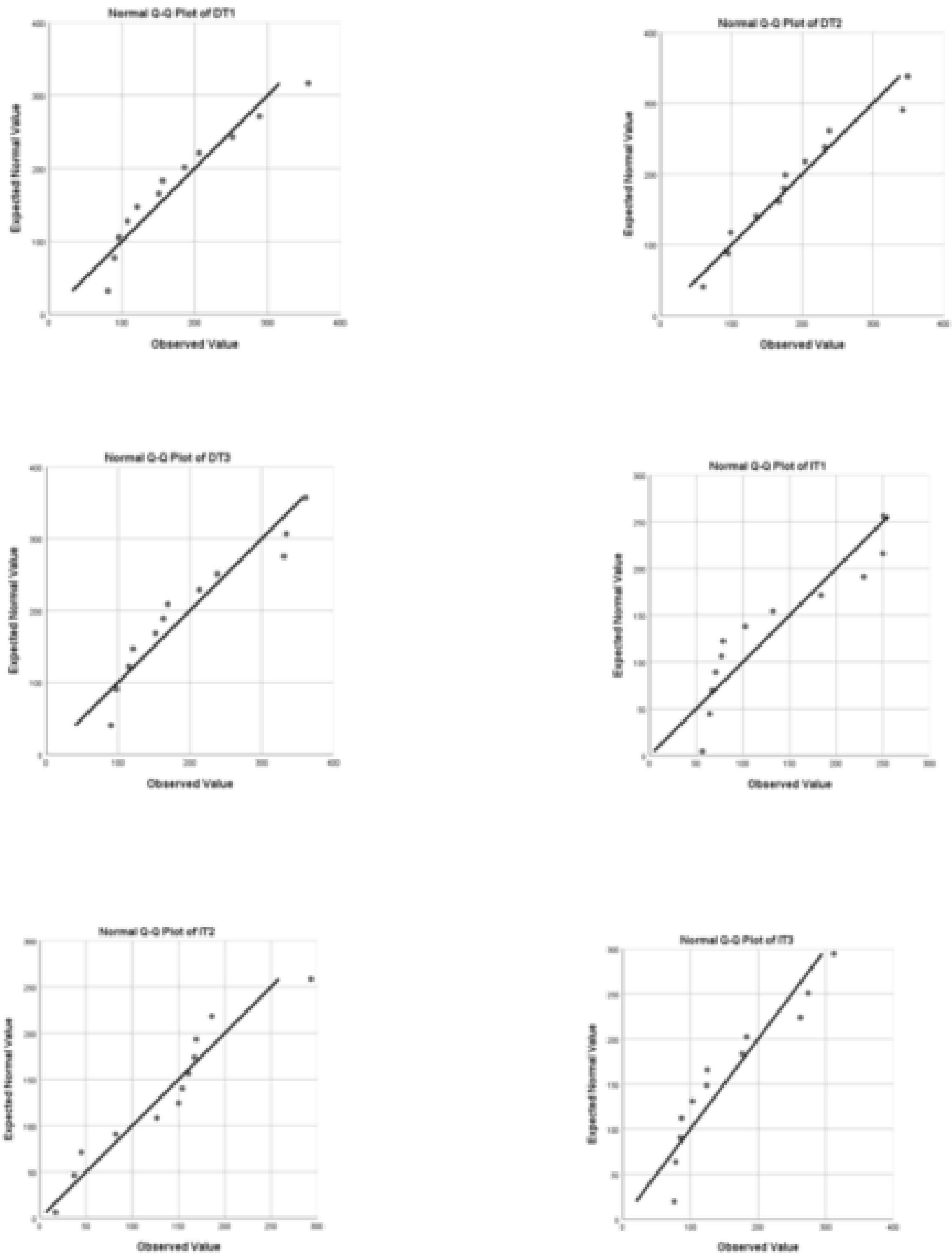


Figure 3.5: Box plot showing approximately normality

Source		F	Sig.
MCA	Sphericity Assumed	18.646	0.001
Volume	Sphericity Assumed	23.812	<0.001

Table 3.4: Overall test within subjects' effect – Dolphin and Invivo

Since the assumptions were met, a parametric test was chosen. In this study, the two dependent variables (MCA and volume) and two independent variables (Invivo and Dolphin), were analyzed using the Multivariate Repeated Measure MANOVA. A pairwise comparison analysis showed a statistically significant mean MCA difference ($p=0.001$) and volume ($p<0.001$) when comparing both software (Tables 3.5 and 3.6). Dolphin showed higher mean average results than Invivo; in the MCA $_{\text{higher average}}$ = 47.533 mm^2 and in Volume $_{\text{higher average}}$ =1.487 cc. The large high CI ranging from 0.816 to 2.158 at 95% shows the low precision of the results between Invivo and Dolphin. There is no interaction between time-points in the MCA nor in volume when evaluating the software. The results drawn through graphs in appendices 3.1 and 3.2 could suggest clinical relevance, even though there were no statistically significant differences.

Measure: MCA

(I) Dolphin	(J) Invivo	Mean Difference (I-J)	Sig.	95% CI for Difference	
				Lower Bound	Upper Bound
1	2	47.553	0.001	23.315	71.791

Table 3.5: Pairwise comparison Dolphin and Invivo for MCA

Measure: Volume

(I) Dolphin	(J) Invivo	Mean Difference (I-J)	Sig.	95% CI for Difference	
				Lower Bound	Upper Bound
1	2	1.487*	0.001	0.816	2.158

Table 3.6: Pairwise comparison Dolphin and Invivo, Volume.

3.4- Discussion

The ICC analysis to evaluate the validity and inter and intra-reliability is a suitable tool to account for measuring agreement or consensus.[40] Compared to Person's r or Spearman's p, ICC is a more appropriate tool because it considers the differences in ratings along with the correlation between examiners.[40,118,119] A recent systematic review on the reliability of assessing upper airway through CBCT showed that among the five high-quality studies included, the upper airway volume evaluation demonstrated moderate-to-excellent intra-reliability (0.780-0.998).[116] On the same review, only three studies showed inter-reliability results, in which they reached an excellent agreement for upper airway volume (0.986-0.998) and moderate-to-excellent inter-reliability for MCA (0.696-0.988).[116] In the present study's agreement, an excellent intra-reliability was attained for the first and second examiner (> 0.93) when volume and MCA of the oropharyngeal space were evaluated using Invivo or Dolphin. Likewise, an excellent inter-reliability between the two examiners was achieved (0.903 to 0.980) in all measurements. Also, the short range of lower and higher CI limits indicate a good agreement (see Table 3.2).[40] Conversely, one previously published study showed poor reliability for MCA among six examiners (0.591), although they found excellent reliability for the oropharyngeal volume among the same six examiners (0.976).[36] Another two studies showed good reliability for cross-sectional area (0.853 and 0.780/0.823).[78,120] Possibly because the oropharynx is described as the easiest portion of the upper airway to be isolated and measured in CBCT reconstructions, with that there are greater chances to achieve good inter and intra reliability results in .[36,39–41,120] The tubular shape of the oropharynx and the irregular anatomy of the nasopharynx and nasal airway can be the reasons for the higher reliability rates on the oropharynx.[39,40] Inter-reliability is as important as intra-reliability to assure diagnostic consistency and accuracy. To satisfy a high-quality requirement of this work, following findings of previous studies showing that experienced examiners have better reliability scores, a second examiner with 15 years of experience in oral radiology was selected to perform the inter-reliability test.[36,121]

Accuracy is measured evaluating how close to a true or accepted value the result is. However, a ground truth value is not established and determined for upper airway volume. One study tentatively evaluated the same sample through a manual segmented technique to compare the results with the ones gathered from the Invivo and Dolphin analysis.[41] The data resulted from the manual segmentation was considered the gold standard; however, they found low accuracy, in some cases exceeding 30% difference between manual and automatic segmentation results.[41] The accuracy can be calculated checking the amount of inaccuracy using the absolute measurement error (ME) which is the difference between a measured quantity and its true value. Since we do not have a true value for oropharyngeal airway volume and oropharyngeal MCA we applied the absolute measurement error analysis to evaluate our results. Our absolute measurement error results showed 0.05 cc or 5.02% for Invivo volume measures, 0.12cc or 11.89% for Dolphin volume measures; 0.15 mm^2 or 14.83% for Invivo MCA and 0.04 mm^2 or 4.30% for Dolphin MCA. These results showed higher uncertain results for oropharyngeal volume measured with Dolphin (11.89%) and MCA measured with Invivo (14.83%). The absence of true values for oropharyngeal volume and MCA makes challenging the translation of these values to clinical implications. The difference between the measurement error results for volume in Invivo and Dolphin seems to be related to the algorithm of each software because the measurement protocol used was the same for all measures. However, the differences between the MCA measures in each software could be related to the chance that the Dolphin gives the examiner to select the area where the software should look for the MCA, avoiding sharp tips of the edges. Invivo, in turn, do not allow this correction.

In this study, Invivo and Dolphin software were used to evaluate the dimensional changes in oropharynx after maxillary expansion. Both use automatic segmentation, with semi-automatic tools to allow the examiner to achieve personal expectations; however, there are some differences in the procedures as following described.

In Invivo software, the airway selection requires that several points need to be picked inside the airway area to develop the airway volume of the selected area, these points generate arrows indicating the area to be covered. For the oropharynx, the points were selected at the level of the hard palate, posterior nasal spine line, level of the soft palate, level of the epiglottis and just below epiglottis; and by double-clicking at the last arrow included, the software understands that that is the selected area. After the creation of the selected airway volume using the arrows, the profile can be modified to adequate to the exact boundaries by clicking on it and editing the spline in the sagittal slice. Then a final airway volume was redrawn and recorded, showing volume and MCA.

Using Dolphin, the selection of the airway is made by clicking on the landmarks to select the wanted boundaries, lines delimitating the selected area will appear, allowing the delimitation of the exact area/volume desired since the first selection. After that, some seed points inside those limits are manually added to select the whole airway volume (Figure 3.5). The MCA area measurements from Dolphin have to be carefully analyzed because in some cases the area selected ends with a sharp end and the minimal cross-sectional area will be defined by the software crossing that sharp area, giving a not accurate result for the MCA for the whole selected space. For this reason, the red dotted line limiting the selected area needed to be checked to assure the accurate selection of the MCA by the software.

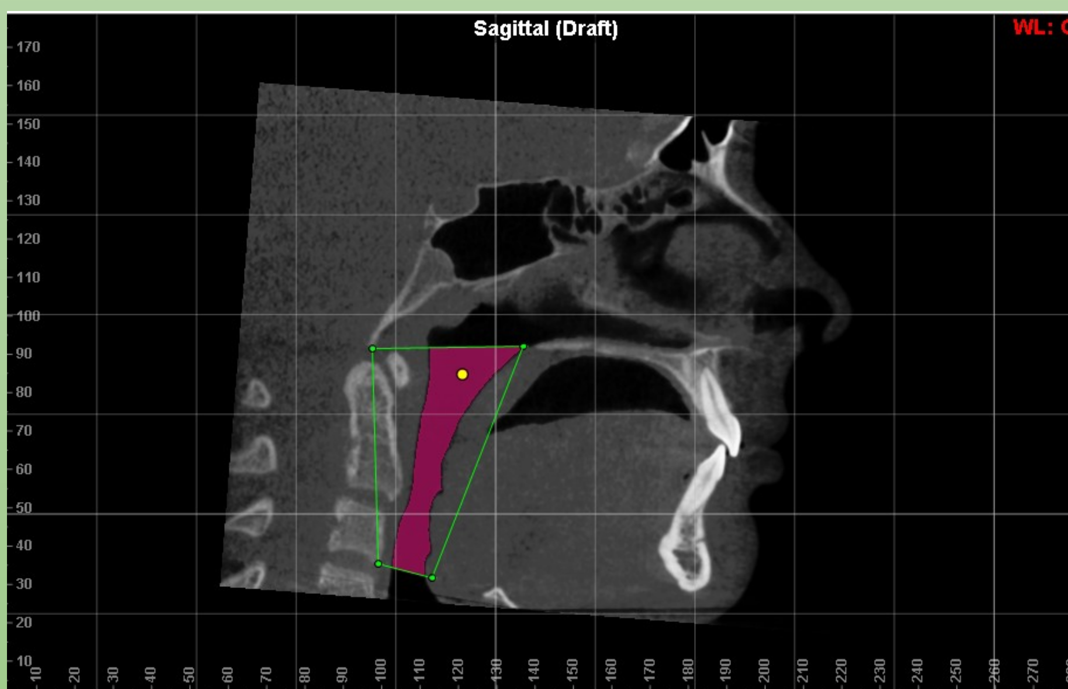


Figure 3.6: Boundaries delimitation and seed point in Dolphin Software

For measurements, both software allows the brightness and contrast adjustment to enhance the image visualization, this procedure aids the better differentiation between bone and soft tissue areas. In addition, both software has tools to control the threshold values, giving the software the density range to fill the airway space. The threshold interval will limit the inclusion of all voxels with grey values within that interval to build the volume.[39] This tool is a so-called Hounsfield Unit;

however, caution is needed to do not mix the terms Hounsfield Unit (HU) and threshold or grey value because the HU is based on the linear attenuation of the tissues on the CT acquisition, and not on the CBCT due to acquisition geometry.

The HU is used to estimate bone density in images derived from multidetector Computed Tomography (MDCT).[122] In most of the CT scans, the HU is set from -1000 to ≥1000, where 0 is water and -1000 is air, i.[17,122] For each image voxel, an HU value will be determined during the image reconstruction, the units are defined as linear transformations of measured X-Ray attenuation coefficients of a material with reference to water.[122] Areas that absorb more X-Rays have a higher HU value.[122] There is a try to convert HU values to bone material density (BMD), using CT or micro-CT.[122] Bone density measurements require a consistent correlation between the grey value (Gy) and bone density. However, HU's use to determine bone density is not recommended for CBCT images because there are important differences between MDCT and CBCT acquisition that makes challenging to correlate and use of quantitative Gy values for CBCTs.[122] A large fluctuation of the Gy values can be seen in CBCTs due to limited field size, relatively high amount of scattered radiation, radiation physics principles, a variation of mass limitations of currently applied reconstruction algorithms.[122] A study performed by Katsumata et al found that the grey levels in a CBCT image varied from -1500 to over 3000.[123] The smaller the CBCTs' field of view the better the resolution and the less radiation dose; however, also less accurate Gy values.[123] Moreover, the Gy values attained on one CBCT scanner may differ from those obtained on another manufacturer's scanners.[123] And even the Gy values acquired from one CBCT may differ from another obtained by the same machine.[123] Some researchers have studied a way to derive grey levels from a CBCT into HU,[123,124] or analyze regression equations to correlate the material density with HU from

CBCT,[125,126] which could be useful to evaluate bone quality in a clinical environment. Therefore, caution is needed to consider the HU values provided by the third party software, moreover, to affirm a certain amount of HU was defined to evaluate upper airway using CBCTs. The software has been using the nomenclature HU linked to airway evaluation, in that sense, perhaps a more correct nomenclature would be threshold or grey value when it refers to CBCT data.

To measure the airway volume in 3D, the desired volume boundaries need to be drawn in several slices, with that, the number of voxels will be measured and a volume derived.[41] The automated software makes this task easier; however, since voxels may have different grey densities within it, the selection of the threshold is a delicate task.[41] The threshold value range to evaluate airway can be very tricky and may give a high variability between measures.[39] The threshold value is important to guide the software to differentiate between soft tissue and air. However, the threshold sensitivity value is very subjective. A previous study demonstrated a poor intra-reliability (0.473) and a poor inter-reliability (0.000-0.100) when evaluating interactive threshold selection (when the threshold is chosen for each scan independently) for upper airway measurement.[36] Similarly, another study showed that having the freedom to determine threshold may influence upper airway segmentation accuracy.[39] Because of this poor reliability for the threshold found in the previous studies, and since the aim of this study is to determine oropharyngeal dimensional changes between different time-points in the same patient and not a true value of the volumetric measurements, a fixed threshold was chosen. This is an attempt to eliminate the examiner's subjectivity and to avoid incurring in greater possibilities of systematic measurement errors among the time-points using different threshold values which could give inaccurate measurements.[39] Moreover, a previous study showed similar oropharyngeal volumetric results among five software when a fixed threshold was applied.[39] As mentioned above, within a voxel different grey values may appear, with that in mind a threshold range needs to be determined. The lower threshold for airway analysis is set automatically by the software around -1000; since this is the value for air.[127] Nakano et al determined in their study an upper threshold for airway when evaluated by CT as -460 to -470.[127] Considering that there is no upper threshold for airway established to be used in CBCTs, and there are differences in HU values between CT and CBCT, we defined the use of - 400 HU to be used in this study.

Our study showed statistically significant differences between Invivo and Dolphin when analyzing MCA and volume ($p \leq 0.001$). Likewise, another study that compared six software encountered statistically significant differences between oropharyngeal volume measurements among Dolphin and Invivo.[39] The difference between software could be attributed to dissimilarities in the software algorithms to identify and fill airway boundaries.[39] Neither one of this two software nor any other software for CBCT analysis of upper airway is considered a gold standard, therefore it was not possible to perform the Bland Altman correlation test that usually points the best "diagnostic tool" when it is compared to a well-established gold standard tool.[128] Some studies have tried to encompass this limitation measuring phantom prototypes and comparing the measurement in different software[39] or comparing the manual segmentation measurement with the automatic ones[41]. Weissheimer et al showed better matching results in Dolphin (1% error) than in Invivo (11% error) when compared to a known phantom volume[39], and El and Palomo study demonstrated better correlation results when Dolphin was compared to a manual segmented technique than when Invivo results were correlated[41]. In our experience, it seems that the inclusion of the arrows to inform the Invivo software where to stop de inferior delimitation below the epiglottis sometimes give not accurate boundaries delimitation to where the last clicks on the arrow were done. In our case, we carefully adjusted the boundaries after the first delimitation by the Invivo software, to match exactly the same boundaries used in Dolphin as described in table 1. Perhaps, the attention to this detail may lead to a more or less accurate result.

3.4.1 Limitations

Even though there are differences between both software, it is not possible to ascertain which one is more accurate because there are no ground values for the oropharyngeal volume and cross-sectional area to compare with the results obtained with the software. One other limitation is the stand position to perform the CBCT exam in which does not enable the analysis of the upper airway in a supine position simulating the same position while sleeping.[8] Ingman et al inferred that a difference in the oropharyngeal area may occur when upright and supine positions are compared, which do not happen to the naso or hypopharyngeal areas.[129] Additionally, there is no validated minimal threshold level for volume and MCA indicating its true values.

3.5- Conclusion

Through the values for inter and intra-reliability, it is possible to observe that both examiners were considered reliable; the intra reliability for both examiners showed results above 90% considered excellent, as well as for inter-reliability. Invivo and Dolphin showed statistically significant different results when evaluating oropharyngeal MCA and volume; however, it was not possible to assume which one would have the most accurate measurement result when compared to the real volume and MCA.

Chapter 4: Oropharyngeal dimensional changes following maxillary expansion with two different appliances: a CBCT study

4.1 – Introduction

Background and Objectives

Breathing is a crucial body function, and its dysfunction requires imperative attention. The etiology of breathing-related problems largely vary, one of them is related to an atypical orofacial growing pattern that can lead to a diminished size of the upper airway (upper respiratory tract). This volumetric reduction may be one of the causes of Sleep-Disordered Breathing (SDB) in children[130]. An atypical orofacial growing pattern may be manifested by a constricted maxilla, usually leading to posterior cross-bites and teeth crowding. On the other hand, SDB can facilitate craniofacial development problems such as narrow maxilla, crossbites, mandibular retrognathia, and clockwise mandibular growth rotation; all of them have been linked to chronic mouth breathing.[40,131–134] The earlier the diagnostic and management is completed, the better the possibilities of normalizing craniofacial development.[34,40]

In 1860, RME was introduced into the scientific literature as an orthodontic option to treat maxillary constriction.[82,135] Maxillary expansion is used to correct posterior crossbites and constricted maxilla, increase the dental arch perimeter[43], potentially alter the upper airway supporting structures[64]. Maxillary expansion can be achieved by either using orthopaedic approaches, orthodontic appliances or performing maxillofacial surgery.[51] RME is a common technique used to manage the constricted maxilla using orthopaedic appliances. The most common RME appliances are fixed (banded or bonded) and have an expansion screw to separate the mid-palate suture. Normal clinical expansion ranges from 3 to10 mm.[72,82] The active phase takes around one month and for the retention phase, approximately 3-6 months is required to allow the re-calcification of the palatal suture.[82] Hyrax is one of the orthopaedic appliances frequently used to manage maxillary dental and/or skeletal constriction through rapid maxillary expansion.[49,50] Moreover, it is the one mostly used in studies evaluating maxillary expansion what can be reassured evaluating a recently published systematic review in which 100% of the included studies used Hyrax. [72]

The Damon self-ligating system was first proposed by Dwight Damon in the 1990s, it is an orthodontic philosophy that is also used to fix transversal discrepancies.[68] The Damon self-ligating system (Ormco, Glendora, CA – US) is a treatment based on light archwire generated forces with, allegedly, faster treatment results, claiming to operate through the concept of stimulating cellular activity without damaging the vascular net of the periodontium.[136] Damon System expansion is categorized as archwire and according to Damon's supporters, considerable expansion can be achieved in the buccal segments, producing a broader arch form.[136] Only a few studies have evaluated the Damon System regarding maxillary expansion, and they claimed that there are differences in pre-molar and molar inter-width after treatment when compared to other conventional self-ligating brackets.[68,70,137] Although some argue those differences could be more related to buccally dental tipping rather than a true skeletal maxillary expansion.[68]

Orthopaedic treatments, such as maxillary protraction and maxillary expansion, have been related to increases in the upper airway volume and MCA.[55,56,64,65,75,76,138,139] However, there is no published scientific evidence regarding similar changes through the Damon philosophical approach. Following the claim from Damon proponents that the therapeutic effect after its use in the narrowed maxilla is a broader dental arch related to alveolar bone remodeling,[140] we speculate if the upper airway volume and MCA could also be increased. Therefore, the primary main objective of this study is to compare the volume and MCA changes in the oropharyngeal space following maxillary expansion using the Damon system and Hyrax appliances, as assessed through CBCT imaging. The second aim is to compare the subjective patients' breathing capacity using the NOSE questionnaire before and after treatment.

4.2 Methods

This project derived from an original study approved by the Health Research Ethics Board, University of Alberta number Pro00013379. The CONSORT statement was used to report methods and results.[141]

Trial design

The trial design of this retrospective analysis of data from a previously conducted randomized clinical controlled trial, parallel, with an allocation ratio of 1:1.

Participants, eligibility criteria and settings

Patients from 11 to 17 years old, with maxillary transverse discrepancies in need of maxillary expansion were included. This is a retrospective analysis of data collected in which patients with unilateral or bilateral posterior crossbites were randomly allocated into one of two treatment groups, Hyrax or Damon approaches, in the orthodontic clinic at the University of Alberta, Edmonton Canada.

Interventions

Patients in the Hyrax group had the appliance cemented with bands and non-self ligating brackets (n-SLB) were placed on upper 3-3 and lower 6-6 (Figure 4.2). The Hyrax appliance was banded on the maxillary permanent first molars and first pre-molars. The expansion screw was activated twice a day, 0.25 mm per turn, (0.50 mm per day) until 20% overcorrection was achieved. After correction achieved, the appliance was left passively for six months as a retention period. After this period, the Hyrax was removed and maxillary first premolars and first molars were bracketed with n-SLB.

The Damon group had full braces installed using Damon Q braces (Figure 4.3). Buttons were fixed on the lingual surface of the upper 6s and 4s, this way crossbites elastics (3/16 inch, 2-ounce force) were used against lower 6s and 4s brackets/tubes. The elastics were used the full time until 20% overcorrection was achieved. At the time overcorrection was achieved, the patient was instructed to wear the elastics at night for 6 months. The archwire sequence used in the first 6 months of treatment was 0.014, 0.016, and 0.018 NiTi wires and by the end of the 6 months had 16x22 NiTi wires.

CBCT scans were taken with I-Cat (Imaging Sciences International, Hatfield, PA, USA) at 120 kVp, 18.54 mA and 8.9 seconds image timing, 0.3 voxel size and 16 x 13 cm FOV. Patients underwent CBCT imaging at two time-points: T1- before treatment and after clinical evaluation, to further evaluate and assist the clinicians on the diagnosis on dental and craniofacial orthodontic discrepancies; T2- after completion of all treatment. All images were taken by one of the two radiology dental assistants, at the radiology clinic of University of Alberta following the standardised protocol for this study. The patients were instructed to stay still with natural head position and Frankfort Plane parallel to the horizontal plane, the patients' head was stabilised with a strip to standardise the head and neck position and to prevent movements. The patients were instructed to maintain the tongue right behind the upper central incisors and in maximum intercuspation. The images reconstructed were stored as DICOM files and made anonymous for blinding purposes.

Outcomes

The CBCT data was assessed through Invivo Software (Anatomage, San Jose, California, US) and Dolphin Software (Dolphin Imaging & Management Solutions, Chatsworth, California US) to check if there were significant differences among the available software. Inter and intra-rater reliability for all the measures was performed using part of the sample, 24 patients' data, 12 Hyrax and 12 Damon.

Sample size calculation

We had assessed to a convenient sample at the pool of CBCTs of the Orthodontic clinic of The University of Alberta. 31 patients were allocated in Damon group and 29 patients were allocated in the Hyrax group. To evaluate the sampling capability we checked the post-hoc power analysis, at a significant level of 0.05.

Randomization: sequence generation, allocation concealment, implementation

With the use of an excel worksheet creating random number blocks, the randomization was done allocating the patients in one of two groups (Hyrax and Damon). After the patient was accepted for the study, the allocation concealment was concluded. A third person designated which orthodontist would perform the treatment, using the Excel random file.

Blinding

It was not possible to blind the patient nor the orthodontist. However, the CBCT data collection and data analysis were blinded since the image exams were coded.

Qualitative assessment of the patients' breathing status

A qualitative assessment was done using the NOSE questionnaire modified from The NOSE Scale 2003, American Academy of Otolaryngology-Head and Neck Surgery Foundation, validated in adult and children populations.[142,143] The NOSE questionnaire comprises of 5 statements regarding Nasal congestion or stuffiness, Nasal blockage or obstruction, Trouble breathing by the nose, Trouble sleeping, Unable to get enough air by nose during exercise or exertion. For each statement, a type Likert Scale consisting of five points ranging from 0 to 4 was used. The patients were instructed how to fill out the questionnaire and the importance of accurate answers. The question "Over the past month, how much of a problem were the following conditions for you?" was valid for the 5 statements. The five possible answers were: Not a problem, Very mild problem, Moderate problem, Fairly bad problem, Severe problem. The questionnaire was applied at T1, and T2.

Statistical analysis

A pilot study tested the reliability of the evaluators using Intraclass correlations at IBM SPSS statistics 25 version. Repeated measures multivariate analysis of variance (MANOVA) and Bonferroni post-hoc tests were used to analyse the differences between the treatment groups at each time-point and each software. A paired-sample t-test was applied to verify whether or not the changes were statistically significant. All the statistical analysis was made at a 5% significance level (95% CI) using IBM SPSS statistics 25 version (SPSS Inc, Chicago, IL). Descriptive statistics were used to assess the Nose questionnaire scores. The results were organized in tables with the absolute frequency (n), and the relative frequency in percentage (proportion). ANOVA Test was applied to analyse NOSE data between groups.

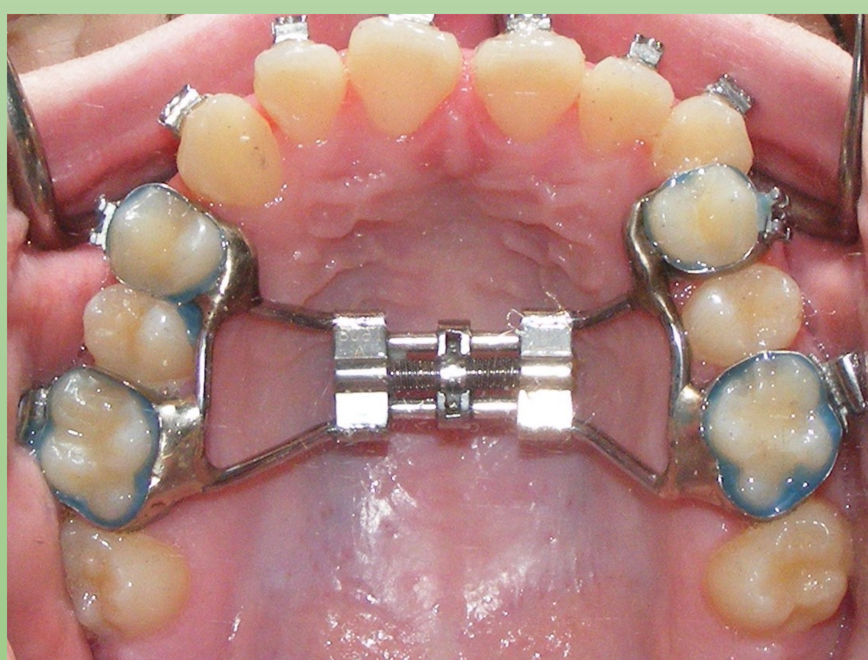


Figure 4.2: RME Hyrax type banded on maxillary 4s and 6s

Figure 4.3: Damon System

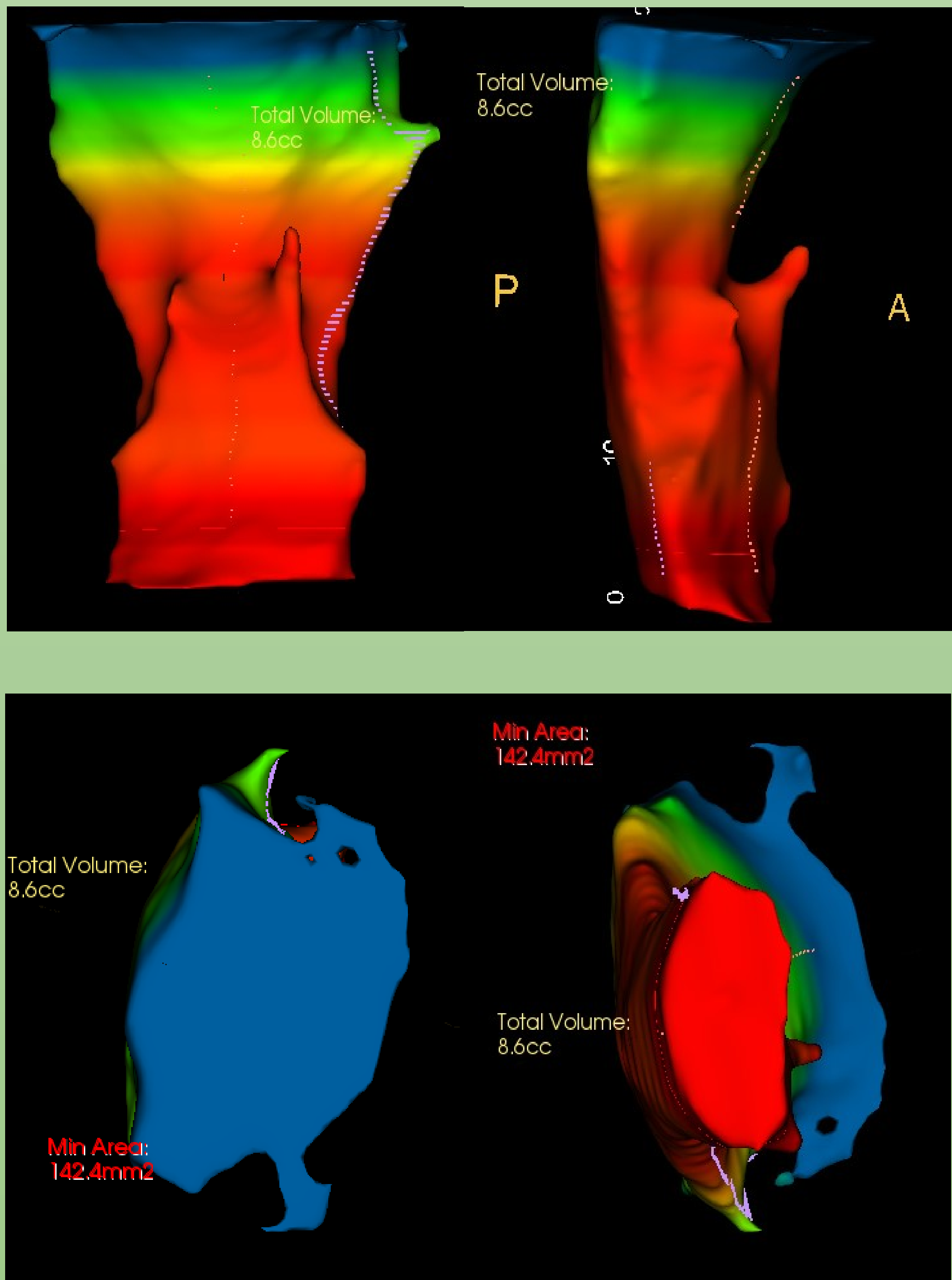


Figure 4.4: Oropharyngeal volume at coronal, sagittal and axial views.

4.3 Results

The 60 patients with unilateral or bilateral posterior crossbites received treatment at the Orthodontic clinics of the University of Alberta between 2011 and 2018; they were randomly allocated in one of two groups, Group 1 treated with a Hyrax (n=29) and Group 2 treated with Damon approach (n=31). The percentage of patients per gender and the average age at time-points across groups are described in table 4.1.

Treatment group	Gender	Average Age at T1	Average Age at T2
Hyrax	58% F and 41% M	13.24y	15.24y
Damon	67% F and 32% M	13.87y	15.97y

Table 4.1: Gender percentage and age average across Hyrax and Damon groups

Our data have three factors: Time with two levels – T1, T2; Appliance with two levels – Hyrax and Damon; Software with two levels – Invivo and Dolphin. The dependent variables are the volume of the oropharyngeal airway in cc, and the MCA of the oropharyngeal airway in mm^2 considered continuous response variables. To determine whether the main effects and interaction effect are statistically significant, an overall test was performed as the first step. Since the overall test showed statistical significance in at least one factor, a parametric or non-parametric test was applied according to the analysis of the assumptions.

The model assumptions were evaluated. According to the box plot, the groups are approximately normally distributed (Figure 1). The Kolmogorov-Smirnov test showed some groups as normally distributed ($p > 0.05$) and some groups as not normally distributed ($p < 0.05$). However, since visually the plots showed an approximated normality, the normality assumption was considered met. Moreover, the center limit theorem reinforced the normality in our study due to sample size >30. At a 5% significant level, the descriptive statistics showed that the overall mean oropharyngeal volume was 12.27 cc at T1 and 14.10 cc at T2. The overall oropharyngeal MCA mean was 123.86 mm^2 at T1 and 141.54 mm^2 at T2. The lowest mean oropharyngeal volume was at T1 in Hyrax group evaluated with Invivo software, 11.341 ± 4.98. The lowest was at T1 in Hyrax group analysed with Invivo, 108.61 ± 59.99.

It is possible to affirm that the observations are independent, which means that the observations are not influenced by each other. On the homogeneity of variances for each combination of the groups of the three independent variables, the sphericity was not violated. For the factor Time, the sphericity test showed a p=0.454 for volume and p=0.604 for MCA. The F test results are: For Time/volume F (2, 116) = 6.332, p=0.02; for Time/minimal cross-sectional area F (2, 116) = 3.306, p=0.04. For time/appliance/volume F (2, 116) = 0.609, p=0.546, for time/appliance/MCA F (2, 116) = 1.223, p=0.298. For the time/software/volume interaction, F (2,116) = 0.850, p=0.430 and time/software/MCA F (2, 116) = 0.242, p=0.785.

Since the assumptions were met, a parametric test was chosen. In this study, there are two dependent variable and three independent variables (factors). Therefore, the parametric test with post-hoc adjustment was applied. A pairwise comparison analysis was evaluated. At a 5% significant level there is no evidence to suggest the treatments generate different results regarding volume (p=0.857) and MCA (p=0.997) when analysing all time-points together. The mean difference was of -0.219 at 95%CI [-2.651, 2.212] for volume and 0.066 at 95% CI [-30.691, 30.823] for MCA (Table 4.2).

			Mean Difference	p-vale	95% Confidence Interval for Difference	
					Lower Bound	Upper Bound
Volume	HYRAX	DAMON	-0.219	0.857	-2.651	2.212
MCA*	HYRAX	DAMON	0.066	0.997	-30.691	30.823

Table 4.2: Pairwise comparison between appliances. * MCA-Minimal Cross-sectional area

While both groups combined, when comparing time-points, the results showed that there is evidence to support that the oropharyngeal volume (p=0.002), and the MCA (p=0.04) are different between time-points. The results of the pairwise comparison test are displayed in Table 4.3. In oropharyngeal volume the Hyrax group when evaluated with Dolphin software showed a significant increase of T2 over T1 in oropharyngeal volume with p=0.005, with an average increase of 2.23cc (18% increase). Oropharyngeal volume in Hyrax group evaluated with Invivo also showed statistically significant results in T2 over T1 with increases of 20% respectively (see table 4.3). Graphs in appendices 4.1 and 4.2 show the relations between appliances and oropharyngeal volume and MCA. Regarding MCA, the Hyrax group measured with Dolphin showed statistically significant increased results in T2 over T1 (23% increase respectively). And MCA increase in the Hyrax group analysed with Invivo in T2 over T1 was seen (26%).

The post-hoc power test showed a low power due to the large standard deviation and a relatively small sample size.

Regarding the NOSE questionnaire, table 4.4 displays all the absolute frequency and the relative frequency of the results. Of the 60 patients, only 33 answered the NOSE questionnaire at the two time-points (55%), Hyrax group (n=14) and Damon group (n=19). Each question has rated from 0-4 according to the answers. The rate was multiplied by 5 to reach a grade from 0-100 from each patient.[144] The severity of nasal obstruction is analysed according to the rate, Mild (5-25), Moderate (30-50), Severe (55-75) and Extreme (80-100) nasal obstruction.[144] No statistically significant results were found showing an improvement in patients' nasal perceived obstruction between T1 and T2 ($p>0.05$, see Tables 4.5 and 4.6).

	ABSOLUT FREQUENCY					PERCENTAGE RELATIVE FREQUENCY (proportion)				
	np	mp	modp	bp	sp	np	mp	modp	bp	sp
NCT1H	4	8	2	0	0	28.60%	57.10%	14.30%	0.00%	0.00%
NBT1H	9	3	1	0	0	69.20%	23.10%	7.70%	0.00%	0.00%
TBT1H	8	5	1	0	0	57.10%	35.70%	7.10%	0.00%	0.00%
TST1H	10	2	2	0	0	71.40%	14.30%	14.30%	0.00%	0.00%
TET1H	10	3	0	1	0	71.40%	21.40%	0.00%	7.10%	0.00%
NCT2H	5	8	1	0	0	35.70%	57.10%	7.10%	0.00%	0.00%
NBT2H	9	5	0	0	0	64.30%	35.70%	0.00%	0.00%	0.00%
TBT2H	10	4	0	0	0	71.40%	28.60%	0.00%	0.00%	0.00%
TST2H	8	2	4	0	0	57.10%	14.30%	28.60%	0.00%	0.00%
TET2H	11	2	1	0	0	78.60%	14.30%	7.10%	0.00%	0.00%
NCT3H	6	5	3	0	0	42.90%	35.70%	21.40%	0.00%	0.00%
NBT3H	9	4	1	0	0	64.30%	28.60%	7.10%	0.00%	0.00%
TBT3H	9	3	2	0	0	64.30%	21.40%	14.30%	0.00%	0.00%
TST3H	13	0	1	0	0	92.90%	0.00%	7.10%	0.00%	0.00%
TET3H	9	5	0	0	0	64.30%	35.70%	0.00%	0.00%	0.00%
NCT1D	1	6	4	0	0	9.10%	54.50%	36.40%	0.00%	0.00%
NBT1D	6	3	1	1	0	54.50%	27.30%	9.10%	9.10%	0.00%
TBT1D	5	1	5	0	0	45.50%	9.10%	45.50%	0.00%	0.00%
TST1D	3	6	2	0	0	27.30%	54.50%	18.20%	0.00%	0.00%
TET1D	7	2	1	1	0	63.60%	18.20%	9.10%	9.10%	0.00%
NCT2D	4	6	0	1	0	36.40%	54.50%	0.00%	9.10%	0.00%
NBT2D	9	1	1	0	0	81.80%	9.10%	9.10%	0.00%	0.00%
TBT2D	7	4	0	0	0	63.60%	36.40%	0.00%	0.00%	0.00%
TST2D	9	1	1	0	0	81.80%	9.10%	9.10%	0.00%	0.00%
TET2D	7	2	2	0	0	63.60%	18.20%	18.20%	0.00%	0.00%
NCT3D	6	5	0	0	0	54.50%	45.50%	0.00%	0.00%	0.00%
NBT3D	9	2	0	0	0	81.80%	18.20%	0.00%	0.00%	0.00%
TBT3D	8	2	1	0	0	72.70%	18.20%	9.10%	0.00%	0.00%
TST3D	8	2	0	1	0	72.70%	18.20%	0.00%	9.10%	0.00%
TET3D	8	1	1	1	0	72.70%	9.10%	9.10%	9.10%	0.00%

Table 4.4: Absolute and relative frequency of NOSE questionnaire. Abbreviations: NC-Nasal congestion or stuffiness, NB- Nasal blockage or obstruction, TB-Trouble breathing through my nose, TS-Trouble sleeping, TE-Unable to get enough air through my nose during exercise or exertion, T1, T2, T3, H=Hyrax, D=Damon

	Time-points			
	1	2	3	Total
N	19	19	19	57
Mean	23.4211	18.4211	16.5789	19.474
Std.Dev.	14.8186	16.8369	17.0825	16.2482

F=0.899
p=0.413

Table 4.5: Summary of Data Damon - NOSE questionnaire

	Time-points			
	1	2	3	Total
N	14	14	14	42
Mean	13.2143	11.4286	10.7143	11.786
Std.Dev.	13.673	10.9945	11.2416	11.7816

F=0.160
p=0.85

Table 4.6: Summary of Data Hyrax - NOSE questionnaire

Treatment	Software	Sample size	Pre-expansion T1 Mean (SD)	Pos-expansion T2 Mean (SD)	Pos-retention T3 Mean (SD)	Change T2-T1 Mean	p-value	Change T3-T1 Mean	p-value	Change T3-T2 Mean	p-value
Damon Volume (cc)	Dolphin	31	13.35 (4.82)	13.69 (4.98)	14.35 (7.17)	0.34	0.695	1	0.311	0.67	0.512
Damon Volume (cc)	Invivo	31	12.06 (4.02)	13.47 (5.22)	13.95 (6.91)	1.41	0.076	1.89	0.067	0.48	0.53
Damon MCA (mm^2)	Dolphin	31	142.52 (69.26)	139.84 (66.18)	149.84 (103.50)	(-)2.68	0.84	7.32	0.643	10.01	0.473
Damon MCA (mm^2)	Invivo	31	118.51 (57.09)	133.95 (68.59)	125.19 (83.10)	15.44	0.22	6.68	0.626	(-)8.76	0.447
Hyrax Volume (cc)	Dolphin	29	12.32 (4.84)	14.61 (5.79)	14.55 (4.89)	2.3	0.004	2.23	0.005	(-)0.66	0.921
Hyrax Volume (cc)	Invivo	29	11.34 (4.98)	13.17 (5.45)	13.58 (4.64)	1.83	0.021	2.24	0.002	0.41	0.533
Hyrax MCA (mm^2)	Dolphin	29	124.93 (67.72)	165.03 (80.74)	154.69 (73.23)	40.1	0.001	29.76	0.007	(-)10.35	0.298
Hyrax MCA (mm^2)	Invivo	29	108.61 (59.99)	119.93 (61.09)	137.02 (67.84)	11.32	0.378	28.41	0.003	17.09	0.217

Table 4.3: Oropharyngeal dimensional changes in T1, T2, T3

4.4 – Discussion

The umbrella review showed in chapter 2 of this thesis, demonstrated a disagreement between studies measuring oropharyngeal dimensional changes, some authors had found no evidence to support an increase in oropharynx after maxillary expansion but others showed the opposite. [61,67,76–79,97] One of the possibilities to the disagreements is the difference in the airway anatomic boundaries that have been selected across studies, this difference may turn the comparisons across studies inaccurate.[91]

Our study showed a statistically significant increase in the oropharyngeal volume when T1 (before treatment) was compared to T2 (after 6 months of treatment), and when T1 was compared to T3 (after completion of orthodontic treatment) in the Hyrax group analysed with both software. The results showed 18% increase in the oropharyngeal volume after expansion (T2-T1) and 20%

increase after the completion of treatment (T3-T1), in the Hyrax group in the Dolphin analysis. Our results also showed a statistically significant increase of 32% in the MCA in the Hyrax group when evaluated with Dolphin software between T1 and T2. Differently, from our results, Kavand et al evaluated the oropharyngeal volume after RME treatment with Hyrax and did not find a significant increase in oropharyngeal volume, most likely because their sample size was half of this present study, and the patient's mean age was one year older than our sample.[145] In addition, their anatomic boundaries were slightly different with the superior boundary being the PSN to the tip of C1 while in our case the superior boundary was the PSN to Basion, those difference could lead to different results and assumptions.[145] Some studies have found increases in the oropharynx; Chang et al found changes in the oropharyngeal retropalatal plane, Iwasaki found an increase in the oropharyngeal retropalatal volume, while Ribeiro et al found increases in the oropharyngeal sagittal and axial areas.[62,76,78]

According to proponents of Damon philosophy, considerable expansion can be achieved in the buccal segments, producing a broader arch form based on alveolar remodeling.[68–70] However, no statistical differences in oropharyngeal volume and MCA between time-points was seen in the Damon group in our study. As far as we know, this is the first study evaluating upper airway dimensional changes in patients treated with Damon approach. Atik and Ciger investigated transverse dimensional changes and alterations in maxillary molar inclination comparing Damon System with conventional self-ligating brackets, but their results showed no differences between treatment types.[68] Although they concluded that despite the absence of an active expansion appliance in the Damon group studied, an increase of the intermolar width similar to that in the conventional group using a quad-helix appliance emphasizes that the Damon system could expand the dental arch without using an auxiliary expansion appliance before fixed appliance therapy.[68] Shook et al showed that there were no differences in the inter-canine or inter-molar width between Damon System or in conventional brackets.[137]

However, the measurement error needs to be accounted for the clinical significance, in a broad view, since the mean oropharyngeal volume gained in the Hyrax group measured with Dolphin was approximately 2.3 cc (an increase of 18%), 0.12 cc of measurement error would represent a variation from 2.18 cc to 2.42 cc in the results. The oropharyngeal volume increase in the Hyrax group analysed with Invivo was of 1.83 cc, taking into account the measurement error of 0.05 cc the variance would be from 1.78 cc to 1.88cc. The MCA increase seen in the Hyrax group measured with Dolphin was 40.1 mm^2, considering a measurement error of 0.04 mm^2 the increase could vary from 40.06 to 40.14 mm^2. In spite of that, no MCA significant results were found in the Hyrax group when measured with Invivo between T1 and T2; but an MCA increase of 26% was seen between T1 and T3 and an increment of 20% in the volume between T1 and T3. A post-hoc power calculation showed a small power for the number of subjects allocated in each tested group when the standard deviation was found high and low differences were found between groups. It would be necessary to have had an increase in Damon group over Hyrax of about 30% to reach a power of 0.8. Instead, Damon showed results 20% smaller than Hyrax.

One of the reasons for an increase in the oropharynx level after the maxillary expansion is the difference in tongue position. It was previously claimed that RME provides the tongue additional superior anterior space associated with a better resting position, which could reduce the chances of pharyngeal collapsibility increasing the pharyngeal space (Figure 4.5).[76,82] The oropharyngeal dimensional changes have been also related to mandibular or maxillary advancements on patients class II and class III respectively.[8] Farronato et al related changes in the lower jaw linked to maxillary expansion; moreover, they related the new position of the lower jaw to an increase in the oropharynx size and volume.[146] The reasoning of these two ideas could possibly be an explanation for the increase in the oropharyngeal volume encountered in our study.

The normal growth obviously has a large influence on the dimensional changes. Since the mean average ages for T1 was 13 y, for T2 was 14 y and for T3 was 15 y, there was still normal growth between all time-points and in both treatment groups that could limit the implications of our findings as normal growth changes were not considered. Although in our study only Hyrax showed a statistically significant increase against Damon group which had subjects with similar age, therefore similar growth rates would be expected; this could be an indication of real oropharyngeal dimensional increase after RME and not only related to normal growth. Moreover, when the Hyrax group is analysed, it seems that the growth peak represented by the Scammon curve did not influence greatly the results, likely because of the mean age of the subjects involved in this study was higher than the peak growth of the lymphoid tissues (13 y, 14 y, and 15 y respectively to T1, T2, T3). Though, more studies evaluating breathing capacity complementing this data would assure these hypotheses. Moreover, the clinical significance needs to be fully evaluated.

Our study suggested that there were no changes when comparing right after 6 months (T2) and after the end of the treatment period in both groups (T3), Hyrax and Damon ($p>0.05$ between T2 and T3) when Dolphin was used to analyse the images. Lagravere et al found that there were better long-term stability changes after maxillary expansion in individuals in the pre-pubertal growth peak than in subjects skeletally more mature,[147] however this comparison was not assessed in this study.

Regarding both software, this study showed they are statistically different, however, no gold standard software exists to permit analysis to know which is more reliable and accurate. Some authors have compared these two software with phantoms analysis using manual segmentation, but found high differences between them; even though Dolphin was one with the closest results to the manual segmentation. Weissheimer et al showed better matching results in Dolphin (1% error) than in Invivo (11% error) when compared to a known phantom volume[39], and El and Palomo study demonstrated better correlation results when Dolphin was compared to a manual segmented technique than when Invivo results were correlated.[41]

Our results on the NOSE questionnaire showed no statistically significant differences between time-points in both treatment groups. Likely because the group of patients at T1 were already characterized in the Mild Nasal Obstruction range. The results showed that the patients were at the Mild Nasal Obstruction range also at T2 and T3 in both treatment groups, suggesting no breathing functional changes. Although there was a decrease in the range in T2 and T3 when compared to T1 in both treatments, there were no statistically significant different results. RME has been related to limited skeletal movement, undesirable tooth movement, root resorption and lack of firm anchorage to get long-term stability.[80] Garret et al, Ghoneima et al, Kartalian et al have reported dental tipping, skeletal expansion, and alveolar bending after the use of RME, being the most part of the expansion due to dental tipping.[46–48] In spite of the lack of statistical significance, the clinical significance of maxillary expansion for breathing improvement should be further investigated.

Limitations

The tongue position is a very important factor to consider when evaluating airway through imaging exams. The tongue movement while swallowing and breathing during acquisition could influence dramatically the airway lumen and as a consequence, the volumetric and MCA results in .[91] On this regard, the faster the CBCT scan, the lesser the chance to incur the image on those tongue movements.[91,120] To control this limitation, our intention was to produce a strict protocol for CBCT to minimize the chances of a different tongue and head positions between exams. Another point of discussion is the upright position usually used to undertake the CBCT examination. The upright position allows the position of the head at the natural head position which is the recommended for baseline assessment of upper airway morphology, although the supine position endorses the airway morphology during sleep, where a collapse of the airway may happen.[91] Also, inflammatory conditions and head posture can influence pharyngeal mucosa volume.[45] Even with a strict protocol, we could perceive some cases with different tongue position between T1, T2, and T3, these events could be the cause for a less significant increase in the MCA.

Regarding radiation exposure, the authors are aware of the approximate 150 µSV of effective radiation dose on each of the 3 CBCT scans and their relative the background radiation. The CBCT radiation effective dose seems to be at least 30% higher than a pan and ceph (26 µSV and 12 µSV respectively) for each time-point in each patient. The patients included in this study are within the pubertal growth age, in which the radiation effective dose would be more detrimental due to the exponential cell growth.

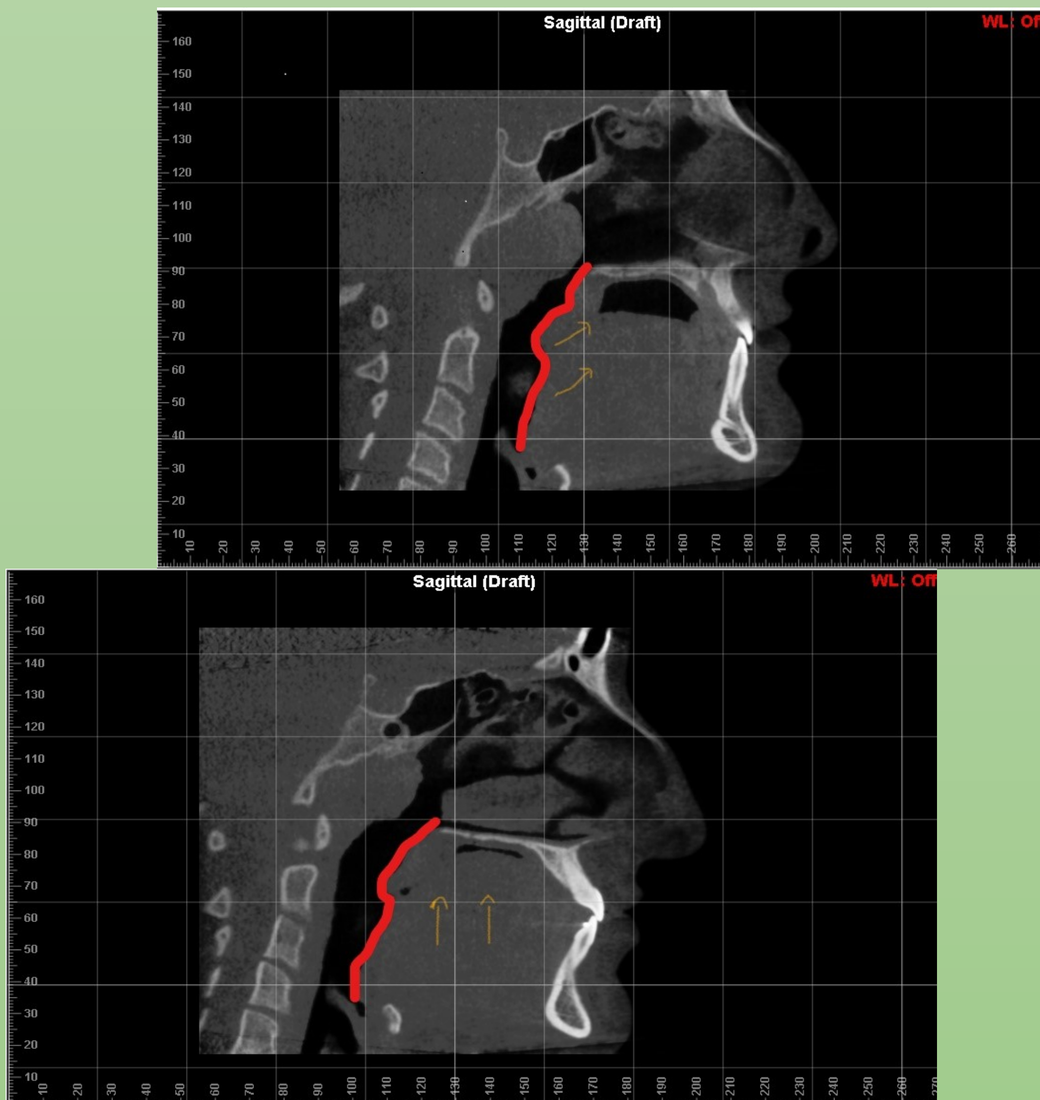


Figure 4.5. Changes in tongue position, after RME the tongue could assume a higher position enlarging the oropharynx volume.

Obesity is an important confounder to OSA and SBD, moreover, obesity can lead to OSA or even can lead to similar symptoms of OSA in children with normal weight due to the fat deposition in the tongue, neck, and geniohyoid and genioglossus muscles.[130] In our study we could not evaluate BMI to link this information to the increase or decrease upper airway dimension.

The absence of a normal control group in our research did not allow the comparison of the growth changes in a similar age group when no appliance was in place permitting changes in the airways. We evaluated simply the oropharyngeal dimensions, studies on the changes in the pharyngeal morphology (shape) after maxillary expansion and the relation of it with breathing capacity could elucidate in a better way this relationship.

4.4.1 Future Research

Future research should focus on airway function to correlate the dimensional changes to airflow and respiratory capacity function after maxillary expansion treatment. As well, the qualitative analysis with patient's feedback by validated questionnaires could elucidate the patient's breathing improvement after orthodontic therapy.

4.5 Conclusion

Statistically significant differences in oropharyngeal volume measurements means within T1/T2 and T1/T3 were identified in the Hyrax group when evaluated with both software and in MCA when evaluated with Dolphin, although no differences for Damon System were found. However, the results found could have no clinical significance when the measurement errors are to be considered and the power effect of the sample was found to be low. NOSE questionnaire did not suggest significant clinical differences in breathing function between time-points nor between treatments. Clinically, there is no minimum volume increase value established in the literature showing effectiveness in the improvement of patients' breathing capacity, more studies are necessary to correlate the volumetric findings to actual quantifiable improvements in breathing.

Chapter 5 – Overall conclusion

A large number of studies have linked RME changes to an increase in the nasal breathing capacity, nasal volume and linear transversal enlargement.[55,60–62,67,82,84] However, inconsistencies between studies' results on nasopharyngeal and oropharyngeal volume and MCA changes after RME lead to uncertainties about the real effect of RME on these upper airway spaces. Therefore, more studies about the oropharyngeal changes related to RME were necessary to understand the real effects of RME in the cited region of the pharynx.

A reliability test was performed to analyse reproducibility and the results showed an excellent agreement inter examiners and intra examiners with all the results above 90%. Hence, answering our first hypothesis, the examiners were reliable, we accepted the null hypothesis.

The analysis among the software Invivo and Dolphin showed statistically significant differences between them. Although there are differences between both software, it was not possible to ascertain which one is more accurate using Bland Altman tests because there are no true values for the oropharyngeal volume and MCA to compare with the results obtained via the software. Therefore the second hypothesis was answered, rejecting the null hypothesis that the software has no statistically differences.

Statistically significant differences in oropharyngeal volume means were found between T1/T2 and T1/T3 in the Hyrax group, rejecting the third null hypothesis. However, regarding clinical significance, the power effect of the sample was found to be low which would require a larger sample to confirm the positive effect of Hyrax over the oropharynx. Although no statistically significant differences were seen in the Damon approach, accepting the fourth null hypothesis.

Nonetheless statistically differences were found between both treatments when time points were evaluated separately, there were no differences in the overall means of the two treatments when all the values were analysed together, answering the fifth hypothesis.

NOSE questionnaire did not suggest significant clinical differences between time-points nor between treatments. Clinically, there is no minimum volume increase value established in the literature showing effectiveness in the improvement of patients' breathing capacity, more studies are necessary to correlate the volumetric findings to actual quantifiable improvements in breathing. Moreover, although RME can influence the breathing capacity of patients with OSA, RME treatment is an auxiliary method[93] and should be used only when orthodontically indicated.

To assure clinically significance is not an easy task, the results found in this work are meant to be analysed carefully. The clinical significance could be implied when the measurement errors are to be considered in the Hyrax group analysed with Dolphin showing an oropharyngeal volume increase between 2.18 to 2.42 cc and 1.78 to 1.88 cc in Invivo. However, the post-hoc power test calculation showed a low power in which would require a larger sample size to confirm the increase in a clinical significance manner.

The variance among the software and the lack of a gold standard tool lead to uncertainties in regards to the results found in this research. Moreover, since there is no minimum volume increase value established in the literature showing effectiveness in the improvement of patients' breathing capacity, more studies are necessary to correlate the volumetric findings to actual quantifiable improvements in breathing.

5.1 Limitation

The stand position to perform the CBCT exam is a limitation which does not enable the analysis of the upper airway in a supine position simulating the same position while sleeping.[8] Also, the patient's position and tongue movement are very important concerns to be considered when evaluating airway through image exams. The tongue movement related to swallowing and breathing can influence dramatically the airway lumen and as a consequence, the upper airway dimensions.[91]

Software differences, especially in MCA, can be related to the possibility of the limitation for the area where the Dolphin will acquire for the MCA, however, Invivo does not enable the same kind of tool. With that, slightly sharp tips on the edges of the boundaries can give the wrong interpretation from the software that there is located the MCA. Dolphin gives an easier and straightway to select the boundaries, whereas Invivo gives arrows that some times, even though clicking at the exact inferior border as described in previous chapters, the selection of the total volume does not comprehend the total portion required, and a second step is necessary to adequate the correct boundaries.

5.2 Future research

Future research should focus on airway function to correlate the dimensional changes to airflow and respiratory capacity function after maxillary expansion treatment. As well, the qualitative analysis with patient's feedback by validated questionnaires could elucidate the patient's breathing improvement after orthodontic therapy.

REFERENCES

1. Strohl KP, Butler JP MA. Mechanical Properties of the Upper Airway. 2013;2(3):1853-1872. doi:10.1002/cphy.c110053.Mechanical

2. Schwab RJ. Upper airway imaging. *Clin Chest Med*. 1998;19(1):33-54.

3. Catlin B, Lyons J, O'Rahilly, Muller, Carpenter, Swenson. Basic Human Anatomy. The pharynx and larynx. Dartmouth Medical School.

4. Kryger MH, Roth T, Dement WC. *Princippl es Ad Practice of Sleep Medicine*. 5 th. (Elsevier Saunders, ed.).; 2011.

5. Hatcher DC. Cone Beam Computed Tomography: Craniofacial and Airway Analysis. *Sleep Med Clin*. 2010;5(1). doi:10.1016/j.cden.2012.02.002

6. Tourné LPM. Growth of the pharynx and its physiologic implications. *Am J Orthod Dentofac Orthop*. 1991;99(2):129-139. doi:10.1016/0889-5406(91)70115-D

7. Doyle WJ, Swarts JD. Eustachian tube-tensor veli palatini muscle-cranial base relationships in children and adults: an osteological study. *Int J Pediatr Otorhinolaryngol*. 2010;74(9):986-990. doi:10.1016/j.ijporl.2010.05.021

8. American Association of Orthodontics TF. *White Paper : Obstructive Sleep Apnea and Orthodontics*.; 2019. www.aaoinfo.org.

9. Scammon R, Harris J, Jackson C, Patterson D. The measurement of man. *Univ Minnesota*

Press. 1930.

10. McNamara Jr JA. Components of class II malocclusion in children 8-10 years of age. *Angle Orthod*. 1981;51(3). https://www.angle.org/doi/pdf/10.1043/0003-3219(1981)051%3C0177%3ACOCIMI%3E2.0.CO%3B2. Accessed February 14, 2019.

11. McNamara Jr JA. Influence of respiratory pattern on craniofacial growth. *Angle Orthod*. 1981;51(4):269-300.

12. Macari AT, Haddad R V. The case for environmental etiology of malocclusion in modern civilizations — Airway morphology and facial growth. *Semin Orthod*. 2016;22(3):223-233. doi:10.1053/j.sodo.2016.05.009

13. Thorpy MJ. Classification of Sleep Disorders. *Neurotherapeutics*. 2012;9:687-701. doi:10.1007/s13311-012-0145-6

14. Perlis M LK. *Treating Sleep Disorders - Principles and Practice of Behavioral Sleep Medicine*.; 2003.

15. Rossini G, Cavallini C, Cassetta M, Barbato E. 3D cephalometric analysis obtained from computed tomography. Review of the literature. *Ann Stomatol (Roma)*. 2011;2(3-4):31-39. http://www.ncbi.nlm.nih.gov/pubmed/22545187. Accessed March 23, 2019.

16. Lenza M de O, Dalstra M, Cattaneo P, Melsen B, Lenza M. An analysis of different approaches to the assessment of upper airway morphology: a CBCT study. *Orthod Craniofac Res*. 2010;13(2):96-105. doi:10.1111/j.1601-6343.2010.01482.x

17. Kapila SD. *Cone Beam Computed Tomography in Orthodontics: Indications, Insights, and Innovations*.; 2014. doi:10.1002/9781118674888

18. Baumrind S, Frantz RC. The reliability of head film measurements. 2. Conventional angular and linear measures. *Am J Orthod*. 1971;60(5):505-517. http://www.ncbi.nlm.nih.gov/pubmed/5286677. Accessed March 31, 2019.

19. Baumrind S, Frantz RC. The reliability of head film measurements. 1. Landmark identification. *Am J Orthod*. 1971;60(2):111-127.

20. Patel A, Bhavra GS, O'Neill JRS. MRI scanning and orthodontics. *J Orthod*. 2006;33(4):246-249. doi:10.1179/146531205225021726

21. Conley RS, Cattaneo PM, Haskell BS. Characterization of the upper airway morphology and its changes in the apneic patient using Cone Beam Computed Tomography. In: *Cone Beam Computed Tomography in Orthodontics: Indications, Insights, and Innovations*. 1st ed. John Wiley & Sons, Inc.; 2014:273-290.

22. Schwab RJ, Pasirstein M, Pierson R, et al. Identification of Upper Airway Anatomic Risk Factors for Obstructive Sleep Apnea with Volumetric Magnetic Resonance Imaging. *Am J Respir Crit Care Med*. 2003;168(5):522-530. doi:10.1164/rccm.200208-866OC

23. Gordon JM, Rosenblatta M, Witmans M, et al. Rapid palatal expansion effects on nasal airway dimensions as measured by acoustic rhinometry. *Angle Orthod*. 2009;79(5):1000-1007. doi:10.2319/082108-441.1

24. El H, Palomo JM. Airway volume for different dentofacial skeletal patterns. *Am J Orthod Dentofac Orthop*. 2011;139(6):e511-e521. doi:10.1016/j.ajodo.2011.02.015

25. McGrath B, Lerman J. Pediatric sleep-disordered breathing: an update on diagnostic testing. *Curr Opin Anaesthesiol*. 2017;30(3):357-361. doi:10.1097/ACO.0000000000000458

26. Li H-Y, Lee L-A. Sleep-disordered breathing in children. *Chang Gung Med J*. 32(3):247-257.

27. Scalzitti N, Hansen S, Maturo S, Lospinoso J, O'Connor P. Comparison of home sleep apnea testing versus laboratory polysomnography for the diagnosis of obstructive sleep apnea in children. *Int J Pediatr Otorhinolaryngol*. 2017;100:44-51.

28. Marcus CL, Chapman D, Ward SD, McColley S. *Clinical Practice Guideline: Diagnosis and Management of Childhood Obstructive Sleep Apnea Syndrome*. Vol 109. American Academy of Pediatrics; 2002. http://www.ncbi.nlm.nih.gov/pubmed/934781. Accessed February 13, 2019.

29. Aurora RN, Zak RS, Karippot A, et al. Practice parameters for the respiratory indications for polysomnography in children. *Sleep*. 2011;34(3):379-388.

30. Mac Donald D. *Oral and Maxillofacial Radiology: A Diagnostic Approach*. West Sussex: Wiley-Blackwell; 2011.

31. Zimmerman JN. Reliability of Upper Pharyngeal Airway Assessment using Dental CBCT. 2017.

32. Scarfe WC, Farman AG. What is Cone-Beam CT and How Does it Work? *Dent Clin North Am*. 2008;52(4):707-730. doi:10.1016/j.cden.2008.05.005

33. Lagravère MO, Low C, Flores-Mir C, et al. Reliability of Traditional Cephalometric Landmarks as Seen in Three-Dimensional Analysis in Maxillary Expansion Treatments. *Angle Orthod*. 2009;79(6):1047-1055. doi:10.2319/010509-10.1

34. Aboudara C, Nielsen I, Huang JC, Maki K, Miller AJ, Hatcher D. Comparison of airway space with conventional lateral headfilms and 3-dimensional reconstruction from cone-beam computed tomography. *Am J Orthod Dentofac Orthop*. 2009;135(4):468-479. doi:10.1016/j.ajodo.2007.04.043

35. Schendel SA, Hatcher D. Automated 3-Dimensional Airway Analysis From Cone-Beam Computed Tomography Data. *J Oral Maxillofac Surg*. 2010;68(3):696-701. doi:10.1016/j.joms.2009.07.040

36. Zimmerman JN, Vora SR, Pliska BT. Reliability of upper airway assessment using CBCT. *Eur J Orthod*. 2018:1-8. doi:10.1093/ejo/cjy058

37. European Commission. CONE BEAM CT FOR DENTAL AND MAXILLOFACIAL RADIOLOGY Evidence-Based Guidelines Directorate-General for Energy Directorate D — Nuclear Energy Unit D4 — Radiation Protection 2012 2. 2012. http://cordis.europa.eu/fp7/euratom/.

38. Miracle AC, Mukherji SK. Conebeam CT of the Head and Neck, Part 1: Physical Principles. *Am J Neuroradiol*. 2009;30(6):1088-1095. doi:10.3174/ajnr.A1653

39. Weissheimer A, Menezes LM De, Sameshima GT, Enciso R, Pham J, Grauer D. Imaging software accuracy for 3-dimensional analysis of the upper airway. *Am J Orthod Dentofac Orthop*. 2012;142(6):801-813. doi:10.1016/j.ajodo.2012.07.015

40. Alsufyani N, Flores-Mir C, Major P. Three-dimensional segmentation of the upper airway using cone beam CT: a systematic review. *Dentomaxillofacial Radiol*. 2012;41(4):276-284. doi:10.1259/dmfr/79433138

41. El H, Palomo JM, Ankara C. Measuring the airway in 3 dimensions: a reliability and accuracy study. *Am J Orthod Dentofacial Orthop*. 2010;137. https://linkinghub.elsevier.com/retrieve/pii/S0889540610000272. Accessed February 28, 2019.

42. Water V, Saridin J, Bouw F, Murawska M, Koudstaal M. Measuring Upper Airway Volume: Accuracy and Reliability of Dolphin 3D Software Compared to Manual Segmentation in Craniosynostosis Patients. *J Oral Maxillofac Surg*. 2014;72:139-144.

43. LaBlonde B, Vich ML, Edwards P, Kula K, Ghoneima A. Three dimensional evaluation of alveolar bone changes in response to different rapid palatal expansion activation rates. *Dental Press J Orthod*. 2017;22(1):89-97. doi:10.1590/2177-6709.22.1.089-097.oar

44. McNamara JA. Early intervention in the transverse dimension: is it worth the effort? *Am J Orthod Dentofacial Orthop*. 2002;121(6):572-574.

45. Nervina JM, Kapila SD, Flores-Mir C. Transverse Deficiency and Treatment Outcomes by Cone Beam Computed Tomography. In: *Cone Beam Computed Tomography in*

Orthodontics: Indications, Insights, and Innovations,. 1st ed. John Wiley & Sons, Inc.; 2014:383-409.

46. Garrett BJ, Caruso JM, Rungcharassaeng K, Farrage JR, Kim JS, Taylor GD. Skeletal effects to the maxilla after rapid maxillary expansion assessed with cone-beam computed tomography. *Am J Orthod Dentofac Orthop*. 2008;134(1):8-9. doi:10.1016/j.ajodo.2008.06.004

47. Ghoneima A, Abdel-Fattah E, Eraso F, Fardo D, Kula K, Hartsfield J. Skeletal and dental changes after rapid maxillary expansion: a computed tomography study. *Aust Orthod J*. 2010;26(2):141-148.

48. Kartalian A, Gohl E, Adamian M, Enciso R. Cone-beam computerized tomography evaluation of the maxillary dentoskeletal complex after rapid palatal expansion. *Am J Orthod Dentofac Orthop*. 2010;138(4):486-492. doi:10.1016/j.ajodo.2008.10.025

49. Cunha AC da, Lee H, Nojima LI, Nojima M da CG, Lee K-J. Miniscrew-assisted rapid palatal expansion for managing arch perimeter in an adult patient. *Dental Press J Orthod*. 2017;22(3):97-108. doi:10.1590/2177-6709.22.3.097-108.oar

50. Farronato G, Giannini L, Galbiati G, Maspero C. Comparison of the dental and skeletal effects of two different rapid palatal expansion appliances for the correction of the maxillary asymmetric transverse discrepancies. *Minerva Stomatol*. 2012;61(3):45-55.

51. Kilic N, Oktay H. Effects of rapid maxillary expansion on nasal breathing and some naso-respiratory and breathing problems in growing children: a literature review. *Int J Pediatr*

Otorhinolaryngol. 2008;72(11):1595-1601. doi:10.1016/j.ijporl.2008.07.014

52. Iwasaki T, Takemoto Y, Inada E, et al. The effect of rapid maxillary expansion on pharyngeal airway pressure during inspiration evaluated using computational fluid dynamics. *Int J Pediatr Otorhinolaryngol*. 2014;78:1258-1264. doi:10.1016/j.ijporl.2014.05.004

53. Iwasaki T, Saitoh I, Takemoto Y, et al. Evaluation of upper airway obstruction in Class II children with fluid-mechanical simulation. *Am J Orthod Dentofac Orthop*. 2011;139:e135-e145. doi:10.1016/j.ajodo.2010.08.014

54. Camacho M, Chang ET, Song SA, et al. Rapid maxillary expansion for pediatric obstructive sleep apnea: A systematic review and meta-analysis. *Laryngoscope*. 2017;127(7):1712-1719. doi:10.1002/lary.26352

55. Pirelli P, Saponara M, Guilleminault C. Rapid maxillary expansion in children with obstructive sleep apnea syndrome. *Sleep*. 2004;27(4):761-766.

56. Villa MP, Rizzoli A, Miano S, Malagola C. Efficacy of rapid maxillary expansion in children with obstructive sleep apnea syndrome: 36 months of follow-up. *Sleep Breath*. 2011;15(2):179-184. doi:10.1007/s11325-011-0505-1

57. Doruk C, Sökücü O, Biçakçi AA, Yilmaz U, Taş F. Comparison of nasal volume changes during rapid maxillary expansion using acoustic rhinometry and computed tomography. *Eur J Orthod*. 2007;29(3):251-255. doi:10.1093/ejo/cjl069

58. Ramires T, Maia RA, Barone JR. Nasal cavity changes and the respiratory standard after maxillary expansion. *Braz J Otorhinolaryngol*. 2008;74(5):763-769. doi:10.1016/S1808-8694(15)31388-4

59. Aras A, Akay MC, Çukurova I, Günbay T, Işıksal E, Aras I. Dimensional Changes of the Nasal Cavity After Transpalatal Distraction Using Bone-Borne Distractor: An Acoustic Rhinometry and Computed Tomography Evaluation. *J Oral Maxillofac Surg*. 2010;68(7):1487-1497. doi:10.1016/j.joms.2009.09.079

60. Zhao Y, Nguyen M, Gohl E, Mah JK, Sameshima G, Enciso R. Oropharyngeal airway changes after rapid palatal expansion evaluated with cone-beam computed tomography. *Am J Orthod Dentofac Orthop*. 2010;137(4):S71-S78. doi:10.1016/j.ajodo.2008.08.026

61. Pangrazio-Kulbersh V, Wine P, Haughey M, Pajtas B, Kaczynski R. Cone beam computed tomography evaluation of changes in the naso-maxillary complex associated with two types of maxillary expanders. *Angle Orthod*. 2012;82(3):448-457. doi:10.2319/072211-464.1

62. Ribeiro ANC, De Paiva JB, Rino-Neto J, Illipronti-Filho E, Trivino T, Fantini SM. Upper airway expansion after rapid maxillary expansion evaluated with cone beam computed tomography. *Angle Orthod*. 2012;82(3):458-463. doi:10.2319/030411-157.1

63. Oliveira De Felippe NL, Da Silveira AC, Viana G, Kusnoto B, Smith B, Evans CA. Relationship between rapid maxillary expansion and nasal cavity size and airway resistance: Short- and long-term effects. *Am J Orthod Dentofac Orthop*. 2008;134(3):370-382. doi:10.1016/j.ajodo.2006.10.034

64. Lotfi V, Ghoneima A, Lagravere M, Kula K, Stewart K. Three-dimensional evaluation of airway volume changes in two expansion activation protocols. *Int Orthod*. 2018;16(1):144-157. doi:10.1016/j.ortho.2018.01.001

65. Mordente CM, Palomo JM, Horta MCR, Souki BQ, Oliveira DD, Andrade IJ. Upper airway assessment using four different maxillary expanders in cleft patients: A cone-beam computed tomography study. *Angle Orthod*. 2016;86(4):617-624. doi:10.2319/032015-174.1

66. Chang YB, Xia JJ, Yuan P, et al. 3D segmentation of maxilla in cone-beam computed tomography imaging using base invariant wavelet active shape model on customized two-manifold topology. *J Xray Sci Technol*. 2013;21(2):251-282. doi:10.3233/XST-130369

67. Zeng J, Gao X. A prospective CBCT study of upper airway changes after rapid maxillary expansion. *Int J Pediatr Otorhinolaryngol*. 2013;77(11):1805-1810. doi:10.1016/j.ijporl.2013.07.028

68. Atik E, Ciğer S. An assessment of conventional and self-ligating brackets in Class I maxillary constriction patients. *Angle Orthod*. 2014;84(4):615-622. doi:10.2319/093013-712.1

69. Vajaria R, BeGole E, Kusnoto B, Galang MT, Obrez A. Evaluation of incisor position and dental transverse dimensional changes using the Damon system. *Angle Orthod*. 2011;81(4):647-652. doi:10.2319/071910-420.1

70. Tecco S, Tetè S, Perillo L, Chimenti C, Festa F. Maxillary arch width changes during

orthodontic treatment with fixed self-ligating and traditional straight-wire appliances. *World J Orthod*. 2009;10(4):290-294. http://www.ncbi.nlm.nih.gov/pubmed/20072744. Accessed February 18, 2019.

71. Schwarting S, Huebers U, Heise M, Schlieper J, Hauschild A. Position paper on the use of mandibular advancement devices in adults with sleep-related breathing disorders: A position paper of the German Society of Dental Sleep Medicine (Deutsche Gesellschaft Zahnaerztliche Schlafmedizin, DGZS). *Sleep Breath*. 2007;11(2):125-126. doi:10.1007/s11325-007-0116-z

72. Buck LM, Dalci O, Ali Darendeliler M, Papageorgiou SN, Papadopoulou AK. Volumetric upper airway changes after rapid maxillary expansion: A systematic review and meta-analysis. *Eur J Orthod*. 2017;39(5):463-473. doi:10.1093/ejo/cjw048

73. Taşpinar F, Uçüncü H, Bishara SE. Rapid maxillary expansion and conductive hearing loss. *Angle Orthod*. 2003;73:669-673.

74. Hartgerink D V., Vig PS, Orth D, Abbott DW. The effect of rapid maxillary expansion on nasal airway resistance. *Am J Orthod Dentofac Orthop*. 1987;92(5):381-389. doi:10.1016/0889-5406(87)90258-7

75. Pirelli P, Saponara M, Attanasio G. Obstructive Sleep Apnoea Syndrome (OSAS) and rhino-tubaric disfunction in children: therapeutic effects of RME therapy. *Prog Orthod*. 2005;6(1):48-61.

76. Iwasaki T, Saitoh I, Takemoto Y, et al. Tongue posture improvement and pharyngeal airway

enlargement as secondary effects of rapid maxillary expansion: A cone-beam computed tomography study. *Am J Orthod Dentofac Orthop*. 2013;143(2):235-245. http://dx.doi.org/10.1016/j.ajodo.2012.09.014. Accessed January 8, 2019.

77. Smith T, Ghoneima A, Stewart K, et al. Three-dimensional computed tomography analysis of airway volume changes after rapid maxillary expansion. *Am J Orthod Dentofac Orthop*. 2012;141:618-626. doi:10.1016/j.ajodo.2011.12.017

78. Chang Y, Koenig LJ, Pruszynski JE, Bradley TG, Bosio JA, Liu D. Dimensional changes of upper airway after rapid maxillary expansion: A prospective cone-beam computed tomography study. *Am J Orthod Dentofac Orthop*. 2013;143(4):462-470. doi:10.1016/j.ajodo.2012.11.019

79. El H, Palomo JM. Three-dimensional evaluation of upper airway following rapid maxillary expansion: A CBCT study. *Angle Orthod*. 2014;84(2):265-273. doi:10.2319/012313-71.1

80. Lagravere M, Carey J, Heo G, Toogood R, Major P. Transverse, vertical, and anteroposterior changes from bone-anchored maxillary expansion vs traditional rapid maxillary expansion: A randomized clinical trial. *Am J Orthod Dentofac Orthop*. 2010;137(3):304.e1-304.e12.

81. Bucci R, Montanaro D, Rongo R, Valletta R, Michelotti A, D'Antò V. Effects of maxillary expansion on the upper airways: Evidence from systematic reviews and meta-analyses. *J Oral Rehabil*. 2019;46(4):377-387. doi:10.1111/joor.12766

82. Huynh NT, Desplats E, Almeida FR. Orthodontics treatments for managing obstructive sleep apnea syndrome in children: A systematic review and meta-analysis. *Sleep Med Rev*.

2016;25:84-94. doi:10.1016/j.smrv.2015.02.002

83. Abdullatif J, Certal V, Zaghi S, et al. Maxillary expansion and maxillomandibular expansion for adult OSA: A systematic review and meta-analysis. *J Cranio-Maxillofacial Surg*. 2016;44(5):574-578. doi:10.1016/j.jcms.2016.02.001

84. Baratieri C, Alves M, De Souza MMG, De Souza Araújo MT, Maia LC. Does rapid maxillary expansion have long-term effects on airway dimensions and breathing? *Am J Orthod Dentofac Orthop*. 2011;140(2):146-156. doi:10.1016/j.ajodo.2011.02.019

85. Alsufyani NA, Noga ML, Witmans M, Major PW. Upper airway imaging in sleep-disordered breathing: role of cone-beam computed tomography. *Oral Radiol*. 2017;33(3):161-169. doi:10.1007/s11282-017-0280-1

86. Grant MJ, Booth A. A typology of reviews: an analysis of 14 review types and associated methodologies. *Health Info Libr J*. 2009;26(2):91-108. doi:10.1111/j.1471-1842.2009.00848.x

87. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (prisma-p) 2015: Elaboration and explanation. *BMJ*. 2015;349:1-25. doi:10.1136/bmj.g7647

88. Moher D et al. Preferred Reporting Items for Systematic review and Meta-Analysis Protocols : The PRISMA Statement. *PLoS Med*. 2009;6(6):e-10.

89. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan—a web and mobile app

for systematic reviews. *Syst Rev*. 2016;5(1):210. doi:10.1186/s13643-016-0384-4

90. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ*. 2017;358:j4008. doi:10.1136/bmj.j4008

91. Di Carlo G, Saccucci M, Ierardo G, et al. Rapid Maxillary Expansion and Upper Airway Morphology: A Systematic Review on the Role of Cone Beam Computed Tomography. *Biomed Res Int*. 2017;2017:1-10. doi:10.1155/2017/5460429

92. Alyessary AS, Othman SA, Yap AUJ, Radzi Z, Rahman MT. Effects of non-surgical rapid maxillary expansion on nasal structures and breathing: A systematic review. *Int Orthod*. 2019;17(1):12-19. doi:10.1016/j.ortho.2019.01.001

93. Vale F, Albergaria M, Carrilho E, et al. Efficay of rapid maxillary expansion in the treatment of Obstruactive Sleep Apnea Syndrome: A Systematic review with meta-analysis. *J Evid Based Dent Pract*. 2017;17(3):159-168.

94. Ortu E, Giannoni M, Ortu M, Gatto R, Monaco A. Oropharyngeal airway changes after rapid maxillary expansion: The state of the art. *Int J Clin Exp Med*. 2014;7(7):1632-1638. doi:10.1016/j.ajodo.2012.11.019

95. Huang WLYTC. Pharyngeal airway changes following maxillary expansion or protraction : A meta- - analysis. 2018;(November 2017):4-11. doi:10.1111/ocr.12208

96. Gordon JM, Rosenblatta M, Witmans M, et al. Rapid palatal expansion effects on nasal

airway dimensions as measured by acoustic rhinometry. *Angle Orthod*. 2009;79(5):1000-1007. doi:10.2319/082108-441.1

97. Almuzian M, Ju X, Almukhtar A, Ayoub A, Al-Muzian L, McDonald JP. Does rapid maxillary expansion affect nasopharyngeal airway? A prospective Cone Beam Computerised Tomography (CBCT) based study. *Surgeon*. 2018;16(1):1-11. doi:10.1016/j.surge.2015.12.006

98. Li L, Qi S, Wang H, Ren S, Ban J. Cone-beam CT evaluation of nasomaxillary complex and upper airway following rapid maxillary expansion. *Zhonghua Kou Qiang Yi Xue Za Zhi*. 2015;50(7):403-407. http://www.ncbi.nlm.nih.gov/pubmed/26564743.

99. Bicakci AA, Agar U, Sökücü O, Babacan H, Doruk C. Nasal airway changes due to rapid maxillary expansion timing. *Angle Orthod*. 2005;75(1):1-6. doi:10.1043/0003-3219(2005)075<0001:NACDTR>2.0.CO;2

100. Izuka EN, Feres MFN, Pignatari SSN. Immediate impact of rapid maxillary expansion on upper airway dimensions and on the quality of life of mouth breathers. *Dental Press J Orthod*. 2015;20(3):43-49. doi:10.1590/2176-9451.20.3.043-049.oar

101. Koudstaal MJ, Poort LJ, van der Wal, K.G. Wolvius EB, Prahl-Andersen, B. Schulten AJ. Surgically assisted rapid maxillary expansion (SARME): a review of the literature. *Int J Oral Maxillofac Surgery,*. 2005;34:709-714.

102. Lagravère MO, Heo G, Major PW, Flores-mir C. Meta-analysis of immediate changes with rapid maxillary expansion treatment. *J Am Dent Assoc*. 2006;137(1):44-53.

doi:10.14219/jada.archive.2006.0020

103. Pirelli P, Saponara M, Guilleminault C. Rapid maxillary expansion (RME) for pediatric obstructive sleep apnea: a 12-year follow-up. *Sleep Med*. 2015;16(8):933-935. doi:10.1016/j.sleep.2015.04.012

104. Martinelli EO, Haddad FLM, Stefanini R, et al. Clinicals And Upper Airway Characteristics in Obese Children with Obstructive Sleep Apnea. *Sleep Sci (Sao Paulo, Brazil)*. 2017;10(1):1-6. doi:10.5935/1984-0063.20170001

105. Haney E, Gansky SA, Lee JS, et al. Comparative analysis of traditional radiographs and cone-beam computed tomography volumetric images in the diagnosis and treatment planning of maxillary impacted canines. *Am J Orthod Dentofacial Orthop*. 2010;137(5):590-597. doi:10.1016/j.ajodo.2008.06.035

106. Botticelli S, Verna C, Cattaneo PM, Heidmann J, Melsen B. Two- versus three-dimensional imaging in subjects with unerupted maxillary canines. *Eur J Orthod*. 2011;33(4):344-349. doi:10.1093/ejo/cjq102

107. Alsufyani NA, Dietrich NH, Lagravère MO, Carey JP, Major PW. Cone beam computed tomography registration for 3-D airway analysis based on anatomic landmarks. *Oral Surgery, Oral Med Oral Pathol Oral Radiol*. 2018;118(3):371-383. doi:10.1016/j.oooo.2014.05.027

108. Yamashina A, Tanimoto K, Sutthiprapaporn P, Hayakawa Y. The reliability of computed tomography (CT) values and dimensional measurements of the oropharyngeal region using

cone beam CT: comparison with multidetector CT. *Dentomaxillofacial Radiol*. 2008;37(5):245-251. doi:10.1259/dmfr/45926904

109. Kim Y-J, Hong J-S, Hwang Y-I, Park Y-H. Three-dimensional analysis of pharyngeal airway in preadolescent children with different anteroposterior skeletal patterns. *Am J Orthod Dentofac Orthop*. 2010;137(3):306.e1-306.e11. doi:10.1016/j.ajodo.2009.10.025

110. Ogawa T, Enciso R, Shintaku WH, Clark GT. Evaluation of cross-section airway configuration of obstructive sleep apnea. *Oral Surgery, Oral Med Oral Pathol Oral Radiol Endodontology*. 2007;103(1):102-108. doi:10.1016/j.tripleo.2006.06.008

111. Masoud AI, Jackson GW, Carley DW. Sleep and airway assessment: A review for dentists. *Cranio - J Craniomandib Pract*. 2017;35(4):206-222. doi:10.1080/08869634.2016.1228440

112. Khojastepour L, Vojdani M, Forghani M. The association between condylar bone changes revealed in cone beam computed tomography and clinical dysfunction index in patients with or without temporomandibular joint disorders. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2017;123(5):600-605. doi:10.1016/j.oooo.2017.01.006

113. Ortiz PM, Tabbaa S, Flores-Mir C, Al-Jewair T. A CBCT Investigation of the Association between Sella-Turcica Bridging and Maxillary Palatal Canine Impaction. *Biomed Res Int*. 2018;2018:1-9. doi:10.1155/2018/4329050

114. Walter SD, Eliasziw M, Donner A. Sample size and optimal designs for reliability studies. *Stat Med*. 1998;17(1):101-110. doi:10.1002/(SICI)1097-0258(19980115)17:1<101::AID-SIM727>3.0.CO;2-E

115. Cevidanes L, Oliveira AEF, Motta A, Phillips C, Burke B, Tyndall D. Head Orientation in CBCT-generated Cephalograms. *Angle Orthod*. 2009;79(5). doi:10.2319/090208-460.1

116. Zimmerman JN, Lee J, Pliska BT. Reliability of upper pharyngeal airway assessment using dental CBCT: A systematic review. *Eur J Orthod*. 2017;39(5):489-496. doi:10.1093/ejo/cjw079

117. Portney LG, Watkins MP. *Foundations of Clinical Research: Applications to Practice*. 3rd Edition. (Pearson, ed.).; 2008. https://www.pearson.com/us/higher-education/program/Portney-Foundations-of-Clinical-Research-Applications-to-Practice-3rd-Edition/PGM274308.html. Accessed February 22, 2019.

118. Müller R, Büttner P. A critical discussion of intraclass correlation coefficients. *Stat Med*. 13(23-24):2465-2476. http://www.ncbi.nlm.nih.gov/pubmed/7701147. Accessed March 29, 2019.

119. Kock GG. Intraclass correaltion coefficient. In: Kotz, S; Johnson NL. In: *Encyclopedia of Statistical Sciences*. 4th ed. Hoboken, NJ: John Wiley & Sons, Ltd; 1982:213-217.

120. Guijarro-Martínez R, Swennen GRJ. Three-dimensional cone beam computed tomography definition of the anatomical subregions of the upper airway: a validation study. *Int J Oral Maxillofac Surg*. 2013;42(9):1140-1149. doi:10.1016/j.ijom.2013.03.007

121. Major MP, Witmans M, El-Hakim H, Major PW, Flores-Mir C. Agreement between cone-beam computed tomography and nasoendoscopy evaluations of adenoid hypertrophy. *Am J Orthod Dentofac Orthop*. 2014;146(4):451-459. doi:10.1016/j.ajodo.2014.06.013

122. Pauwels R, Jacobs R, Singer SR, Mupparapu M. CBCT-based bone quality assessment: are Hounsfield units applicable? *Dentomaxillofac Radiol*. 2015;44(1):20140238. doi:10.1259/dmfr.20140238

123. Katsumata A, Hirukawa A, Okumura S, et al. Relationship between density variability and imaging volume size in cone-beam computerized tomographic scanning of the maxillofacial region: an in vitro study. *Oral Surgery, Oral Med Oral Pathol Oral Radiol Endodontology*. 2009;107(3):420-425. doi:10.1016/j.tripleo.2008.05.049

124. Reeves TE, Mah P, McDavid WD. Deriving Hounsfield units using grey levels in cone beam CT: a clinical application. *Dentomaxillofac Radiol*. 2012;41(6):500-508. doi:10.1259/dmfr/31640433

125. Lagravère MO, Carey J, Ben-Zvi M, Packota G V, Major PW. Effect of object location on the density measurement and Hounsfield conversion in a NewTom 3G cone beam computed tomography unit. *Dentomaxillofac Radiol*. 2008;37(6):305-308. doi:10.1259/dmfr/65993482

126. Lagravère M, Fang Y, Carey J, Toogood R, Packota G, Major P. Density conversion factor determined using a cone-beam computed tomography unit NewTom QR-DVT 9000. *Dentomaxillofacial Radiol*. 2006;35(6):407-409. doi:10.1259/dmfr/55276404

127. Nakano H, Mishima K, Ueda Y, et al. A new method for determining the optimal CT threshold for extracting the upper airway. *Dentomaxillofac Radiol*. 2013;42(3):26397438. doi:10.1259/dmfr/26397438

128. Altman DG, Bland JM. Measurement in Medicine: The Analysis of Method Comparison Studies. *Stat*. 1983;32(3):307. doi:10.2307/2987937

129. Ingman T, Nieminen T, Hurmerinta K. Cephalometric comparison of pharyngeal changes in subjects with upper airway resistance syndrome or obstructive sleep apnoea in upright and supine positions. *Eur J Orthod*. 2004;26(3):321-326.

130. Huang Y-S, Guilleminault C. Pediatric Obstructive Sleep Apnea: Where Do We Stand? *Adv Otorhinolaryngol*. 2017;80:136-144. doi:10.1159/000470885

131. McCrillis JM, Haskell J, Haskell BS, et al. Obstructive Sleep Apnea and the Use of Cone Beam Computed Tomography in Airway Imaging: A Review. *Semin Orthod*. 2009;15(1):63-69. doi:10.1053/j.sodo.2008.09.008

132. Abramson Z, Susarla SM, Lawler M, Bouchard C, Troulis M, Kaban LB. Three-Dimensional Computed Tomographic Airway Analysis of Patients With Obstructive Sleep Apnea Treated by Maxillomandibular Advancement. *J Oral Maxillofac Surg*. 2011;69(3):677-686. doi:10.1016/j.joms.2010.11.037

133. Miles PG, Vig PS, Weyant RJ, Forrest TD, Rockette HE. Craniofacial structure and obstructive sleep apnea syndrome--a qualitative analysis and meta-analysis of the literature. *Am J Orthod Dentofacial Orthop*. 1996;109(2):163-172.

134. Yu X, Fujimoto K, Urushibata K, Matsuzawa Y, Kubo K. Cephalometric analysis in obese and nonobese patients with obstructive sleep apnea syndrome. *Chest*. 2003;124(1):212-218.

135. Angell E. Treatment of irregularities of the permanent or adult tooth. *Dent Cosm*. 1860;1:540-544.

136. Damon D. DamonSystem The Workbook. 2003.

137. Shook C, Kim SM, Burnheimer J, Sohyon ;, Kim M, Burnheimer J. Maxillary arch width and buccal corridor changes with Damon and conventional brackets: A retrospective analysis. *Angle Orthod*. 2016;86(4):655-660. doi:10.2319/050515-304.1

138. Bouserhal J, Bassil-Nassif N, Tauk A, Will L, Limme M. Three-dimensional changes of the naso-maxillary complex following rapid maxillary expansion. doi:10.2319/011313-36.1

139. Iwasaki T, Saitoh I, Takemoto Y, et al. Improvement of nasal airway ventilation after rapid maxillary expansion evaluated with computational fluid dynamics. 2012. doi:10.1016/j.ajodo.2011.08.025

140. Bogdan F, Barron T. A Practical Treatment Objective: Alveolar Bone Modeling with a Fixed, Continuous-Arch Appliance. *Clin impressions®*. 2017;20(1):4-21.

141. Schulz K, Altman D, Moher D. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. *BMJ*. 2010;340(C332).

142. Stewart MG, Witsell DL, Smith TL, Weaver EM, Yueh B, Hannley MT. Development and Validation of the Nasal Obstruction Symptom Evaluation (NOSE) Scale. *Otolaryngol Neck Surg*. 2004;130(2):157-163. doi:10.1016/j.otohns.2003.09.016

143. Zicari AM, Occasi F, Giulia M, et al. Intranasal budesonide in children affected by persistent

allergic rhinitis and its effect on nasal patency and Nasal Obstruction Symptom Evaluation (NOSE) score. *Curr Med Res Opin*. 2015;31(3):391-396. doi:10.1185/03007995.2015.1009532

144. Lipan MJ, Most SP. Development of a Severity Classification System for Subjective Nasal Obstruction. *JAMA Facial Plast Surg*. 2013;15(5):358. doi:10.1001/jamafacial.2013.344

145. Kavand G, Lagravere M, Kulac K, Stewartd K, Ghoneimae A. Retrospective CBCT analysis of airway volume changes after bone-borne vs tooth-borne rapid maxillary expansion. *Angle Orthod*. 2019;online ver.

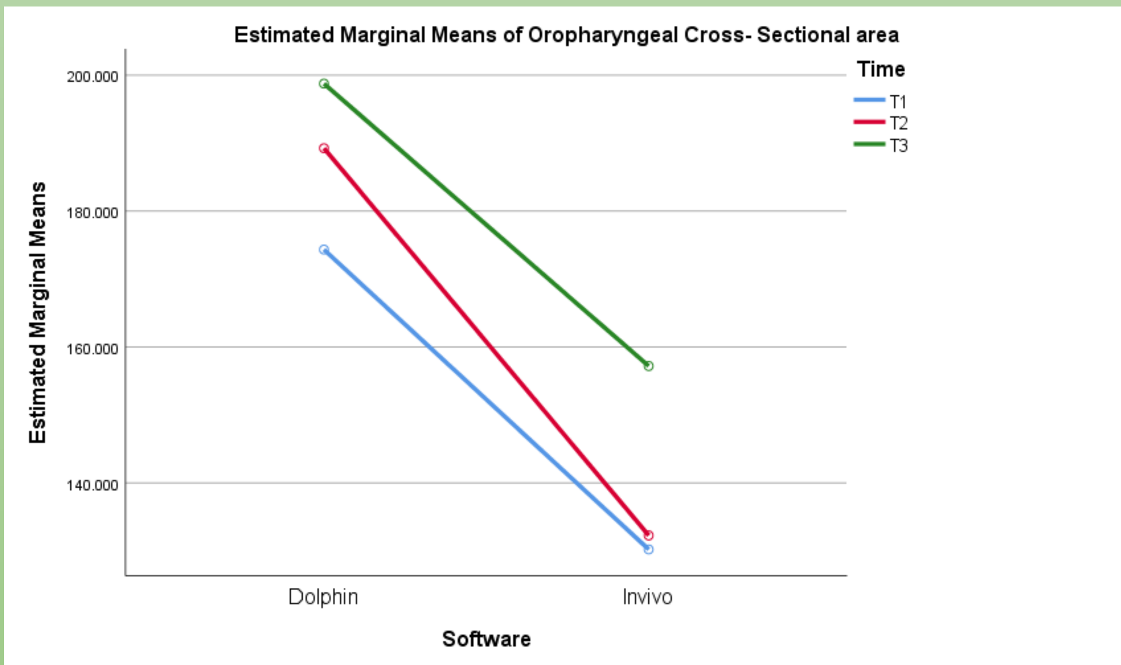
146. Farronato G, Giannini L, Galbiati G, Maspero C. Sagittal and vertical effects of rapid maxillary expansion in Class I, II, and III occlusions. *Angle Orthod*. 2011;81(2):298-303. doi:10.2319/050410-241.1

147. Lagravere M, Major P, Flores-Mir C. Long-term Skeletal Changes with Rapid Maxillary Expansion: A Systematic Review. *Angle Orthod*. 2005;75(6).

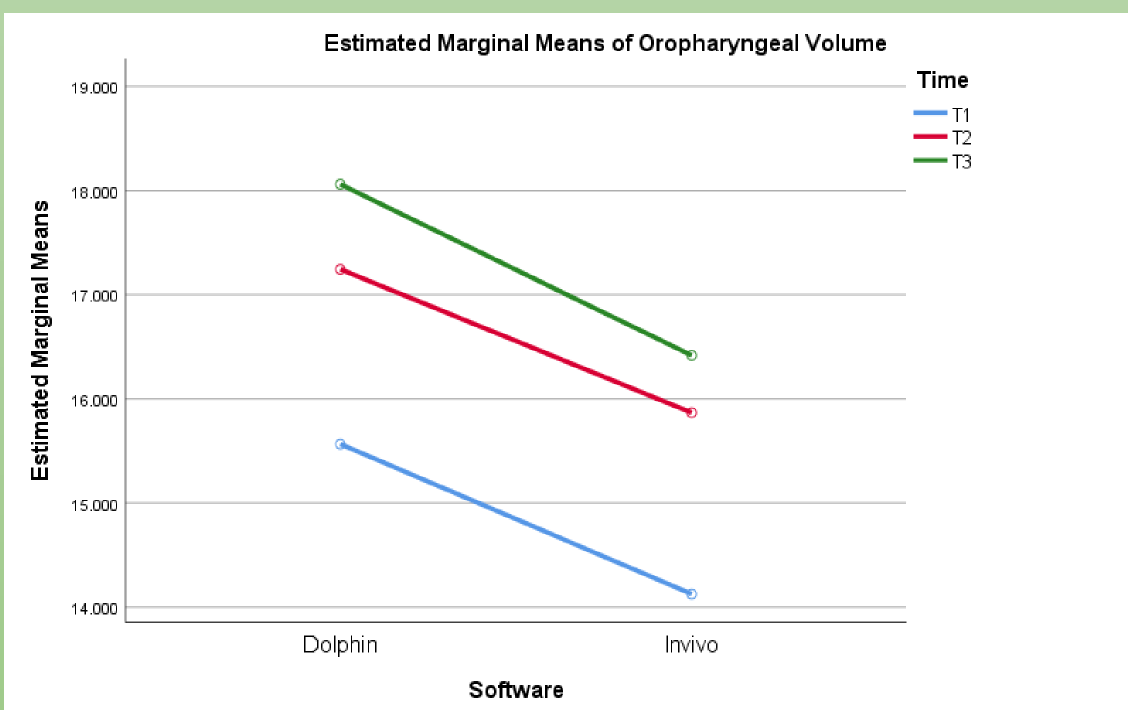
APPENDIX

Appendix 2.1 – Databases and individualized truncations of words

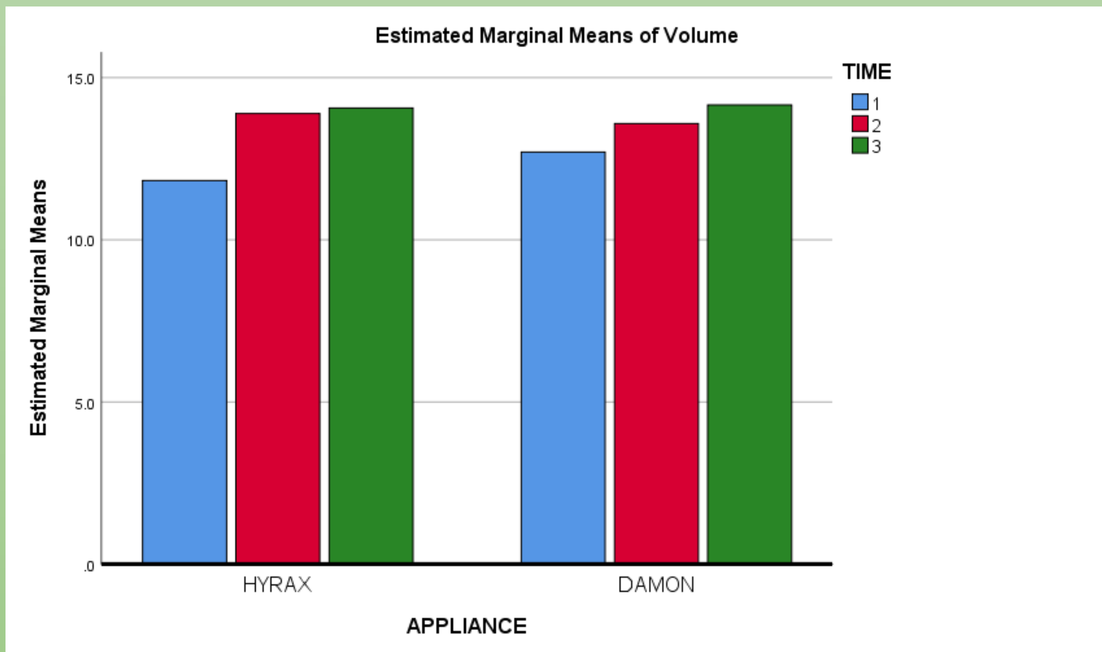
Database ***(Up to April 4, 2019)***	***Key words & search truncation***
MedLine (N= 16) (Ovid) **EMBASE (N= 24)** (Ovid) http://ovidsp.tx.ovid.com	(Palatal Expansion Technique OR ((maxil* or palat*) adj2 expan*).mp OR RME.mp. OR hyrax.mp OR damon.mp. OR exp rapid maxillary expansion OR rapid maxil* expans*.mp) AND ((Nasal Cavity OR Pharynx OR (airway* or nasal or oropharyngeal or oro-pharyn* or pharyn* or nose or nasopharyn* or naso-pharyn*).mp) AND SYSTEMATIC REVIEW.mp. or exp "Systematic Review"
PubMed (N= 18) http://www.ncbi.nln.nih.gov/pubmed	(((((((airway[All Fields] OR (upper airway[All Fields] OR upper airways[All Fields])) OR (nasal[All Fields]) OR nasalpharangyal[All Fields] OR nasalpharyngeal[All Fields] OR nasalpharynx[All Fields])) OR (pharyn[All Fields]) OR (oropharyn[All Fields]) OR ("nose"[MeSH Terms] OR "nose"[All Fields])) OR (nasal pharyngeal[All Fields] OR nasal pharynx[All Fields])) AND ((((("palate"[MeSH Terms] OR "palate"[All Fields] OR "palatal"[All Fields]) AND expansion[All Fields]) OR (("maxilla"[MeSH Terms] OR "maxilla"[All Fields]) AND expansion[All Fields])) OR (("maxilla"[MeSH Terms] OR "maxilla"[All Fields]) AND expansion[All Fields])) OR ("palatal expansion technique"[MeSH Terms] OR ("palatal"[All Fields] AND "expansion"[All Fields] AND "technique"[All Fields]) OR "palatal expansion technique"[All Fields] OR ("maxillary"[All Fields] AND "expansion"[All Fields]) OR "maxillary expansion"[All Fields])) OR (maxil[All Fields] OR maxil2[All Fields] OR maxila[All Fields]) OR (palat[All Fields] OR palata[All Fields] AND (expan[All Fields]) AND "humans"[MeSH Terms]))) AND systematic review
Cochrane (N= 8**)** http://onlinelibrary.wiley.com.login.ezproxy.library.ualberta.ca/cochranelibrary/search/advanced	maxil* expansion or palat* expansion and airway* or upper airway or pharyn*



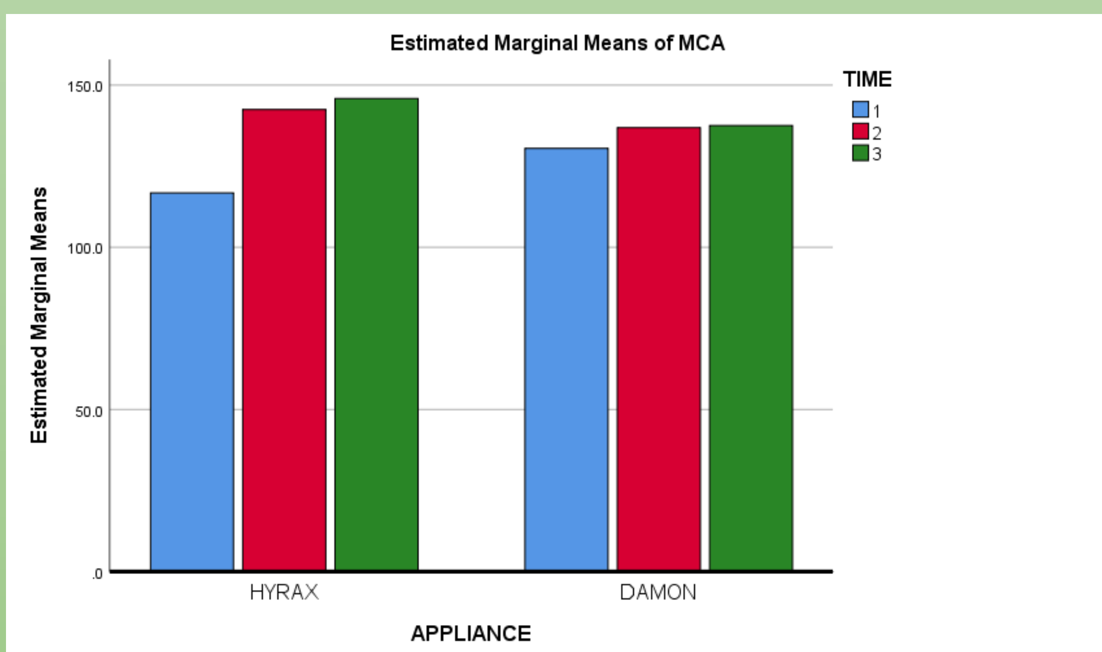
Appendix 3.1: Graph MCA anlysed in both software



Appendix 3.2: Graph Volume analysed in both software



Appendix 4.1: Oropharyngeal volume changes between time-points in Hyrax and Damon



Appendix 4.2: Oropharyngeal MCA changes between time-points