Evaluation of anatomic surgical outcomes in children with sleep disordered breathing symptoms using Cone Beam computed tomography

by

Noura A. Alsufyani

A thesis submitted in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

Medical Sciences - Dentistry
University of Alberta

Abstract

Aims: to utilize accurate and time-efficient methods to segment the upper airway, develop a registration method for longitudinal CBCT data specific for the upper airways, and correlate meaningful CBCT imaging parameters with surgical outcomes in pediatric cohort with SDB symptoms.

Methods: 1) Reliability of several craniofacial landmarks to superimpose upper airway using CBCT images was tested along with impact of plane reorientation based on these landmarks on the upper airway in single and longitudinal CBCT images. 2) A semi-automatic segmentation program for the upper airway was developed and its reliability, validity and time efficiency were tested. 3) Using the previous tools, the upper airways of 10 children/adolescents with SDB symptoms and jaw disproportions were analyzed and correlated with the impact on quality of life survey OSA-18, before and after adenoidectomy or tonsillectomy.

Results: 1) The landmarks chosen were reliable and coordinate transformation significantly reduced measurement errors in longitudinal CBCT data and highlighted large errors in the airways with large neck flexion or tongue malposition. 2) The developed semi-automatic segmentation program was reliable, accurate, and time-efficient. 3) Using point-based analyses, new airway measures were more explanatory than conventional global measures such as volume, strongly correlated with OSA-18 and better explained low scores after surgery.

Conclusions: The semi-automatic segmentation program and registration technique of CBCT upper airways provided reliable tools to test the surgical outcomes in a cohort of children with SDB symptoms. New point-based analysis was complimentary to conventional measures of airway variables and better correlated with clinical measures.

Table of Contents:

Acknowledgment

To my supervisory committee members Drs. Paul Major, Michelle Noga, Manisha Witmans, and Irene Cheng, thank you for your expertise, time, and advice throughout this thesis.

I would like to thankfully acknowledge the full scholarship throughout this PhD provided by King Saud University and Ministry of Higher Education, Riyadh, Saudi Arabia.

My dear friend *Bev*, thank you for sharing this journey with me.

To my dear parents, *Ahmed and Afrah*, I am indebted to you for who I am today. This is dedicated to you.

My dear husband, *Mohammed***,** I am thankful for all the love, support, and encouragement.

To my lovely darlings, *Sara, Layan, and Nof*, I am grateful to share my life with you. You are, and will remain, my greatest accomplishments.

Chapter 1: Introduction

1.1 Literature Review

1.1.1 Pathophysiology of Pediatric Sleep Disorder Breathing (SDB)

Sleep-disordered breathing (SDB) is a spectrum of conditions with abnormal respiratory pattern and/or decreases in oxyhemoglobin saturation during sleep. The spectrum ranges from habitual snoring, upper airway resistance syndrome, to partial or complete airway obstruction termed obstructive sleep apnea (OSA). Habitual snoring has been reported in 3–12% of the general pediatric population and 1–3% will have OSA.[1-3]

Increased upper airway resistance is an essential component of OSA, including any combination of soft tissue narrowing or encroachment of surrounding craniofacial structures. The stability of the upper airway is compromised not only by anatomic factors but abnormalities in neuromuscular activation, ventilator control, and arousal threshold are parts of this complex spectrum. For normal nasal breathing, the air needs to flow from the anterior nasal nares, to the nasal cavity, naso-pharynx, oro-pharynx, hypo-pharynx, and finally to the larynx and lungs (i.e. lower airway). During its journey from the nose to the lungs, the air faces multiple anatomic and neuromuscular factors that may hinder its passage. Having this process during sleep, sets multiple factors into play. In non-snoring, normal children obstructive apneas (complete airway obstruction) and hypopneas (partial airway obstruction) rarely occur, inspiratory flow limitation and respiratory effort–related arousals are uncommon, and oxygen saturation rarely drops below 90%.[4] Children with habitual snoring lack apnea, hypopnea, respiratory effort–related arousals, and gas exchange abnormalities. Children with OSA present with recurrent episodes of partial or complete airway obstruction.[4] The upper airway resistance syndrome (UARS) is characterized by brief, repetitive respiratory effort–related arousals during sleep in the absence of overt apnea,

hypopnea, or gas exchange abnormalities. The fact that (UARS) is a distinct entity however is debated that it is in fact a continuum between habitual snoring and OSA.[5]

Oxygen and carbon dioxide (CO_2) tensions are regulated within narrow limits during wakefulness. In children with and without OSA and during sleep, it is the carbon dioxide that controls the central respiratory drive. The patency of the upper airway is maintained by the balance between the viscoelastic properties of the pharynx, neuromuscular activity, and pressure gradient through the airway (also referred to as transmural pressure). During wakefulness, pharyngeal dilator muscles are active and a stable ventilatory pattern is present. The normal sleep/wake cycle is divided into non-rapid eye movement (NREM) sleep (stages 1, 2, 3) and REM (rapid eye movement) sleep. The deepest stage (stage 3 of NREM) is required for the physically restorative effects of sleep and preadolescent growth. NREM stage 2 and REM are more associated with mental recovery and maintenance.

Some evidence suggests that sympathetic activity is up-regulated in children with OSA causing increased apnea frequency in NREM stage 2 and REM.[6] Upon the transition from awake to non-rapid eye movement sleep (NREM), the diaphragm and muscles of the upper airway show reductions in activity, hypoventilation (two to five folds), and increase in upper airway resistance.[7] In REM, these parameters start to reverse to levels above those noted in NREM sleep or quiet wakefulness with significant increase in sympathetic drive, with increases in heart rate and blood pressure. In the cases where an obstructive event, in a predisposed airway, causes blood oxygen levels to fall, or the physical exertion to breathe is too great, neurological mechanisms trigger a sudden interruption of sleep, called a neurological arousal which further worsens ventilatory instability and cause obstructive cycling.[4] Of the pharyngeal dilator muscles, including the genioglossus, hyoglossus, and styloglossus, the genioglossus is the most easily

measured and was shown to produce forward movement of the tongue, increasing oropharyngeal airway size and stiffness in children.[6]

During sleep, most children with OSA intermittently re-establish stable breathing pattern. This suggests that anatomic measures of the airway lumen, soft tissue, and skeleton are critical to the development of SDB, however do not completely account for it. Dynamic inspiratory airway narrowing during tidal breathing was much greater in children with OSA compared with normal control subjects and upper airway resistance correlated with the severity of OSA in children.[8-11] Children with OSA also had increased collapsibility at the level of the soft palate and retroglossal area compared to normal children, indicating a generalized increased collapsibility of the pharynx.[12]

Inflammation is also thought to be contributing to the development of SDB. It is hypothesized that snoring causes local injury, via prolonged vibration, and induces a mucosal inflammatory response resulting in nerve damage and swelling consequently affecting upper airway resistance and/or collapsibility.[13] These changes were associated with increased expression of leukotriene receptors in tonsillar tissue from children with OSA compared to children with recurrent throat infections and treatment studies using intranasal corticosteroids or leukotriene receptor antagonists resulted in a reduction in OSA severity.[13-15]

1.1.2 Upper airway anatomy

The skeletal support for airway is provided by the cranial base (superiorly), spine (posteriorly), nasal septum (anterosuperiorly), jaws, and hyoid bone (anteriorly), Figure 1.1. The airway valves include the soft palate, tongue, and epiglottis. The upper airway mainly consists of the nasal cavity and the pharynx. The pharyngeal airway is divided into three components: naso-pharynx, oro-pharynx, and hypopharynx, Figure 1.1. The nasopharynx marks the pharyngeal airway posterior to the nasal cavity and usually contains the adenoids and is bounded by the posterior nasal aperture antero-superiorly and the tip of the soft palate inferiorly. The oro-pharynx marks the pharyngeal airway posterior to the oral cavity and contains the tonsils and is bordered by the tongue anteriorly, tip of the soft palate superiorly, and the tip of epiglottis inferiorly. Finally, the hypopharynx marks a small part of the pharynx bordered by the tip of epiglottis superiorly and opens into the larynx and esophagus inferiorly.

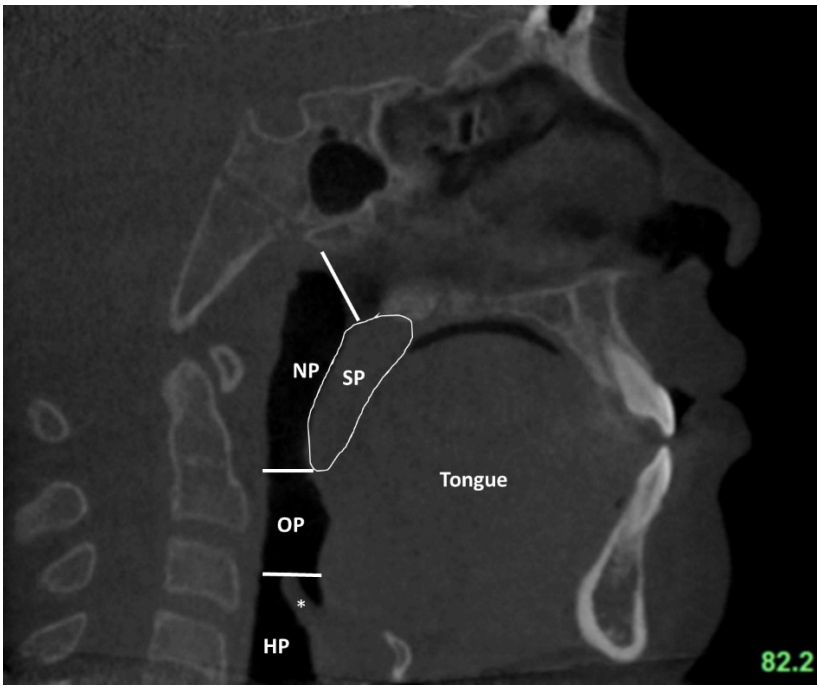


Figure 1.1: Sagittal CBCT image showing upper airway. NP: nasopharynx, OP: oropharynx, HP: hypopharynx, SP: soft palate, *: shows epiglottis.

The nose is formed by three paired structures; inferior, middle, and superior turbinates, with the nasal septum dividing these pairs into right and left. The three paired turbinates will house three paired nasal meatuses through which air flows, Figure 1.2. The boundaries of the nasal cavity are: the anterior nares anteriorly, the posterior nares/aperture posteriorly, the hard palate inferiorly, ethmoid and frontal sinuses superiorly, and the paired maxillary sinuses laterally, Figure 1.2.

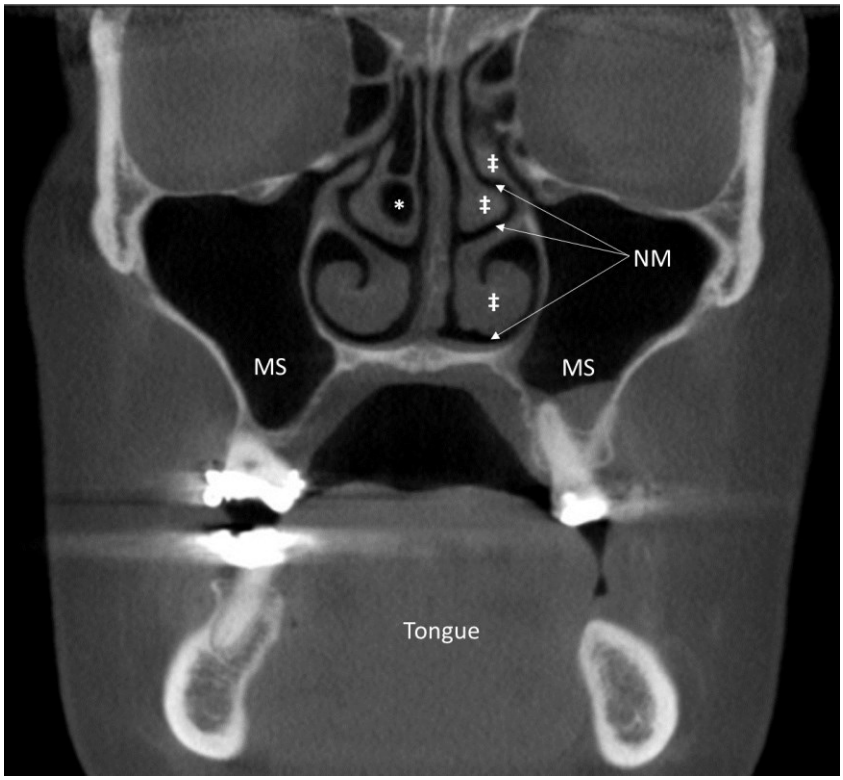


Figure 1.2: Coronal CBCT image showing nasal airway. NM: nasal meatus (inferior, middle, and superior), MS: maxillary sinus, ‡ shows nasal concha (inferior, middle, and superior), *: shows concha bullosa.

While SDB is complex and multi-factorial, upper airway narrowing due to adenotonsillar hypertrophy is considered the main culprit to which treatment is geared towards. Adenoidal tissue, palatine and lingual tonsils, together with other lymphoid tissue forming Waldeyer's ring,

serve as the first line of defense against infections through the nasal and oral cavities. In a healthy child, adenoid enlargement is a physiologic phenomenon and is at its largest size between the ages of 5-10, then decreases in size until adulthood.[16, 17]

Children with OSA have larger adenoid, tonsils and soft palate compared to their controls.[4] Their size correlated with apnea-hypopnea index (AHI) in young children (1.9-9.3 years) and cross-sectional areas at the levels of tonsils and soft palate explained 74.3% of variations in AHI in older children (7-12).[18, 19] Other causes of nasal airway narrowing include allergic rhinitis, turbinate hypertrophy, concha bullosa, deviated septum, and other pathologies such as nasal polyps.[6] The turbinates are paired structures located within the nasal cavity, also called nasal concha, that assist with several functions such as insulation and filtering the inhaled air. Enlargement of the turbinates along with (allergic) rhinitis can impede the air flow through the nose, Figure 1.2. When air from ethmoid air cells pneumatizes within a turbinate of the nose, a concha bullosa is evident. It is considered an anatomical variant however if it reaches a large size, it can locally affect the patency of the nasal airway, Figure 1.2. In a retrospective review of 998 sinus-computed tomography scans, 44% presented with at least one concha bullosa and 79% were associated with deviated nasal septum.[20] It is estimated that 80% of all nasal septums are off-center and mild deviations are normal variants. A "deviated septum" occurs when the septum is severely shifted away from the midline causing localized narrowing of the nasal airway and affecting air flow.[21]

1.1.3 SDB and Craniofacial development

Longitudinal studies on SDB children and experimental data from infant monkeys (in the 1980s)[22-26] are strongly suggestive of an association between normal-breathing, oral-facial muscle tone, normal development of the nasomaxillary complex and mandible.[27]

Presence of abnormal muscle tone due to genetic or environmental reasons in humans, or experimentally induction of abnormal nasal resistance in infant monkeys, is associated with mouth breathing.[27] Human infants prefer breathing through the nose however, are able to breathe through the mouth if the nose is blocked but not for significant lengths of time, due to the weakness of the muscles required to open the oral airway.[28]

At birth, the face is about 40% of adult size, increasing to 65% at 3-6 years of age, about 90% by 11–12 years, and is only completed after puberty.[27, 29] To breathe through the mouth, a child would lower the mandible, leading to anterior positioning of the tongue, resulting in a high-arched palate, narrow maxilla, retrognathia, thus promoting backwards (clockwise) rotation of the mandible, increase lower facial height, and inevitably influence dentoalveolar morphology; features collectively forming the "adenoid facies" or "long face syndrome".[30-36]

1.1.4 SDB risk Factors

Although considerable evidence supports the notion that upper airway obstruction and mouth breathing induce morphologic skeletal changes in the maxilla and mandible, such skeletal changes could further exacerbate the upper airway narrowing thus serving as risk factor.[4] Furthermore, craniofacial features reducing airway were implicated as the

reason for incomplete resolution of SDB to the surgical removal of adenotonsillar tissues, i.e. adenotonsillectmy (AT).[31]

Obesity has tripled since 1980s and the risk of OSA in obese children is at 36%, reaching 60% in the presence of snoring.[4] Obese children also presented with high perioperative complications (such as pain and hemorrhage) and residual OSA post AT.[37-39] Studies suggest that older, obese children with SDB present with adult-like SDB characterized by excessive daytime sleepiness, arousals, sleep fragmentation, and high end-organ dysfunction.[40] Interestingly, obese children with OSA showed more obstructive events in the supine position whereas in non-obese children with OSA, obstructive events were more noted in the prone or side positions.[41] This suggests that sleep posture may affect airway collapsibility, and although lateral positioning increased the size of the adult airway on magnetic resonance imaging (MRI), the degree of neck flexion was not quantified but such data is not available in children.[42]

Another, modest, risk factor is Gastroesophageal reflux disease (GERD). GERD represents the backwards flow of gastric acid to the pharynx. Because acid clearance mechanisms (such as swallowing, salivation and primary esophageal motility) are impaired during sleep, the acid contact time increases.[43] The relationship between sleep problems and GERD is reciprocal; acid irritation causes airway edema and thus narrowing and vice versa, SDB can aggravate GER due to increased negative intra-thoracic pressure.[44] The issue is complex and further studies are needed to investigate sleep architecture and brain function in GERD patients that is not detected by traditional polysomnography.[43, 44]

Multiple risk factors to the development or incomplete resolution of SDB have been identified in the literature such as African race (craniofacial structure and socio-economic

reasons), male (no explanation in children), prematurity (neurologic impairment and adverse craniofacial growth), neurologic disorders (abnormal motor control), environmental (smoking, pets, indoor allergens), family history OSAS (inherited craniofacial structures, neuromusculartureture compensation, arousal threshold, and ventilator control).[29] Depending on the sample size, age range, and study design, the statistical significance of these risk factors vary.

1.1.5 SDB sequelae

SDB is being recognized as the cause of serious morbidities in children including metabolic, cardiovascular, and neurocognitive consequences. Failure to thrive possibly due to reduction in insulin growth factor, obesity and metabolic syndrome, neuropsychological dysfunction (impacting cognition, hyperactivity, sleepiness, low attention and school performance and overall behaviour), cardiovascular abnormalities (autonomic dysfunction, blood pressure abnormalities), elevated serum levels of tumor necrosis factor, C-reactive protein, and interleukins have been documented.[29, 30, 35, 40, 45, 46]

1.1.6 SDB diagnostic tools

Overnight polysomnography (PSG) is considered as the gold standard to establish the existence and severity of disorders during sleep. Apnea-hypopnea index (AHI) determines the severity of OSA during PSG by measuring collapsibility of the upper airway and is a combined magnitude for the amount of collapses and partial collapses or flow limitations of the upper airway during one hour of sleep.[7] Most commonly an AHI of <1-5/hour constitutes mild OSA, 5-10/hour is moderate OSA, and >10 is severe OSA. To that end, different methods in the

determination of the AHI and its thresholds are known to give different results.[29] Moreover, PSG is expensive, time consuming, labor intensive, and limited institutions can use full PSG to diagnose and evaluate pediatric SDB. In Canada, there are 100 sleep labs and 15 of these are in Western Canada with wait times reaching 12-14 months.[47] In Alberta (2001 census population 3,113,586), there are 5 sleep labs and the rate of sleep studies completed per year per 100,000 of population is 96.[47]

The restricted access to PSG, in Canada and worldwide,[47] variability in determination of AHI or other PSG measures, and the need for better methods to diagnose and assess treatment response have initiated a wide search for alternatives.[29]

Portable monitoring (PM) equipment, or home PSG, is portable, unattended monitor that includes at least four channels (airflow, respiratory movements, oxyhemoglobin saturation [SpO_2] and heart rate). While its use has been validated in the adult population and is emerging as a promising tool in children, its validity in diagnosing children for OSA remains contradictory and further research is needed.[48-50]

Nocturnal or overnight pulse oximetry (PO) is a test that involves applying a plastic clip over the fingertip to measure arterial oxygen saturation (SaO_2) to determine the cardiorespiratory stability. Pulse oximetry records two channels: one for oxygen levels, the other for pulse rate. Normal oxygen saturation levels in children are usually between 96-100%. Periodic clusters of desaturation on continuous overnight recording of oxygen saturation with three or more desaturations less than 90% has been demonstrated to have a 97% positive predictive value for OSA in otherwise healthy children.[51] This lead to the development, and validation against PSG, of the McGill Oximetry scoring system by Nixon et al.[52] A McGill score of 1 (SaO_2 drops below

90% <3 times) indicates normal or inconclusive for OSA, a score of 2 (SaO_2 drops below 90% ≥3 times) is indicative of mild OSA, a score of 3 (SaO_2 drops below 90% ≥3 times and below 85% >3 times) indicative of moderate OSA, and score of 4 (SaO_2 drops below 90% ≥3 times, below 85% >3 times and below 80% >3 times) indicative of severe OSA. Scores 1 through 4 deemed recommendations to: further evaluate to rule out OSA, adenotonsillectomy (AT) on the waiting list, AT within 2 weeks, and urgent surgery within days, respectively. However, some disadvantages are worth mentioning. It is conducted under non-expert supervision, i.e. the parents, and the readings can be affected due to child movement. Most importantly, PO has low negative predictive value (high false negative) probably due to the fact that partial airway obstruction is often associated with lesser oxygen desaturation than obstructive apnea which cannot be detected by PO.[53]

Nasopharygoscopy (a video endoscope of the nose and pharynx) is considered the gold standard to examine the adenoids and dynamic changes in the upper airway and the utilization of a standardized grading system has been shown to have high efficacy for diagnosis of airway obstruction.[54] Although reliable, nasopharyngoscopy studies do not measure changes in the upper airway anatomy and their results are based on the subjective analyses of clinicians resulting in inter-observer variations. [55, 56] Consequently, they are unable to quantify the degree of airway obstruction or assess treatment outcome objectively.

Subjective reporting of symptoms are also considered important indicative of the diagnosis. There are multiple surveys and questionnaires developed specific to the OSA diagnosis and impact on quality of life. In a 2014 meta-analysis, it was evident that Pediatric Sleep Questionnaire (PSQ) was a valid instrument to screen for pediatric SDB.[57] The PSQ is a parent filled questionnaire to assess sleep related breathing disorders (SRBD) and symptom for

children aged 2-18 years. The instrument was designed as a broad clinical screen for research purposes by Chervin and co-workers.[58] It has 4 subscales (total 69 items), an important subscale is the Sleep related breathing disorder (SRBD) with 22-item score with sensitivity of 0.85 and specificity of 0.87 for SRBD scale.[58]

Another common survey is that measuring quality of life in OSA-children to quantify impact on emotional state, physical symptoms, and family interaction and that is the Obstructive sleep apnea 18-items Quality of Life Questionnaire (OSA-18).[59] It consists of 18 items divided into five subscales: sleep disturbance, physical symptoms, emotional distress, daytime function, and caregiver concerns, and each item is scored with a 7-point ordinal scale. The OSA- 18 total score ranges from 18 (no impact on quality of life) to 126 (major or severe impact). According to Franco et al. children with OSA-18 total scores below 60 imply a mild impact on quality of life; scores between 60 and 80 imply a moderate impact; and scores exceeding 80 imply a large impact.[59] Using OSA-18 to diagnose or detect OSA in children was contradictory. While few reports found good correlation between OSA-18 and PSG (the gold standard)[60, 61], most studies seem to agree that OSA-18 has poor validity compared to PSG.[57, 62-64] However, the OSA-18 questionnaire was not developed as a diagnostic tool, rather as a disease-specific quality-of-life survey. This is shown by its wide use as an outcome parameter in several studies[65-67] on OSA in children and "even if the OSA-18 does not detect and diagnose pediatric OSA accurately, it may measure other dimensions of the disease than the PSG does"[64]. Others suggested that perhaps PSG measures other than AHI, such as the arousal index or the number and severity of oxygen desaturations, more closely correlate to other postoperative sleep parameters.[68]

In a recent randomized clinical trial of childhood adenotonsillectomy (CHAT), Osa-18 and PSQ at baseline correlated well with AHI or ODI (oxygen desaturation index). Both the PSQ

and OSA-18 along with Race (African American), and obesity (body mass index *z* score > 2) were associated with higher levels of AHI and ODI ($P < .05$) however only explained <3% of variations in AHI or ODI.[69] Given the fact that 55% of the studied children (n=453) were African American (age from 5 to 9.9 years), it is possible this impacted the results of their regression model such that "race" was more significant than tonsillar size. Due to the complex nature of SDB and the multiple potential co-factors that need to be addressed, a significantly large sample size maybe required to accommodate such variability in studies of pediatric SDB. Until then, contradicting studies of the pediatric SDB will continue on emerging.

Interestingly, when a questionnaire is augmented with other tests or physical examination, the performance of the OSA diagnostic test improved.[57] The set of clinical assessment, PSQ along with pulse-oximetry screening provided excellent specificity 98.1%, 94.1% positive predictive value, and performed better in moderate to severe OSA.[70] Good correlation was found between PSQ-sleepiness subscale and objective multiple sleep latency test (MSLT).[71] In fact, using PSG results as the sole indicator for effectiveness of AT in pediatric OSA may neglect other benefits highlighted by quality of life questionnaires that are important to children and their parents.[72]

The optimal methodology and criteria for the diagnosis of SDB in children has not been established. Based on the presented evidence, combining physical exam, validated subjective patient reporting survey, and at least one objective measure (e.g. PO) is far from being a gold standard however, has proven to be reasonable tools in the absence of a full PSG.

1.1.7 SDB Treatment

Non-Surgical therapy

There is no clear consensus on which severity of childhood OSA would warrant treatment. As such, choosing therapy depends on the etiology, severity, history, and available treatment options available.[29]

Topical intranasal steroids have been shown to reduce adenoid hypertrophy and improve scores of obstructed breathing however their long-term success has not been established.[29]

Continuous positive airway pressure (CPAP) is a non-invasive device that delivers mild air pressure through the nose and/or mouth to keep the airways open during sleep. Although it is effective for pediatric OSA, long-term compliance is challenging and side effects include skin erythema, eye irritation, congestion, and maxillary growth impairment as the elastic strap provides restraining force on the maxilla similar to orthodontic head gear.[29, 73, 74]

Maxillary expansion, by means of dental orthodontic appliance, opens the midpalatal suture transversely, widens the maxilla and nasal cavity. This allows the tongue greater space and more forward positioning. After four months of therapy, rapid maxillary expansion (RME) was shown to decrease nasal resistance and improve OSA in children, i.e. AHI reduction, with maxillary constriction, long term efficacy data is however insufficient.[29] Several studies have shown that RME or bimaxillary distraction improve OSA in children or resolve the residual symptoms after adenotonsillectomy.[75-82]

Mandibular anterior repositioning appliances (to modify class II growth)[83, 84] or Protraction face mask (to advance the maxilla in class III growth)[85-90] are not common to treat

pediatric SDB. By moving the mandible or maxilla forward, the airway dimensions enlarged and SDB symptoms improved in different studies in children with OSA. Although these results are encouraging, child compliance is always a hindrance, long term success is not clear, large samples with robust design are definitely in demand.

Surgical therapy

While lymphatic tissues normally regress in volume after the age of 6, the hypertrophic tonsillar and adenoid tissue maybe so large that normal tissue reduction is insufficient to remove the obstruction.[91]

Adenoidectomy and tonsillectomy is the surgical excision of adenoid and tonsillar tissues, respectively. Although the American Academy of Paediatrics recommends adenotonsillectomy (AT) as first line of treatment[92], there is no consensus on whether the adenoids, tonsils, or both need to be removed.[29] Following AT, children with OSA have reported improvements in quality of life, behavior, attention, growth, cognitive scores, and school performance.[29] A recent randomized controlled trial for OSA in school-age children (the CHAT) revealed that AT reduced symptoms and improved behavior, quality of life, and PSG findings however did not significantly improve attention or executive function as measured by neuropsychological testing compared to watchful waiting.[93] Moreover, complete normalization of 110 children with OSA (age 6.4 ± 3.9 years) after AT in only 25% of patients (AHI< 1), 46% with persistent mild OSA (1 >AHI<5), and 29% having at least moderate OSA (AHI> 5).[94] Similarly, Guilleminault and coworkers reported that 45% of OSA children had persistent OSA after adenotonsillectomy.[95] A meta-analysis of AT cure rate of in pediatric OSA was 60%, based on achieving AHI<1.[96]

Residual OSA and perioperative complications, such as post-operative hemorrhage, respiratory difficulties, cardiorespiratory arrest, and anesthetic complications, initiated multiple studies to search for demographic, clinical, and anatomical factors that can be predictive of such negative outcomes. For example, obesity and AHI were identified as possible predictors of residual OSA[94] so did Mallampati score 3 and 4, retrognathic mandible, hypertrophy of nasal inferior turbinates, and deviated septum.[95] Other possible factors associated with residual pediatric OSA were African ethnicity, asthma, family history of SDB, prematurity, chronic rhinitis, and GERD.[77, 97-100] Together, these studies indicate that adenotonsillar hypertrophy is only one of several important determinants of OSA in children.

Supplementing AT with other therapies have shown improvement in selected OSA populations such as turbinectomy, septal repair, intranasal corticosteroids, proton-pump inhibitors, rapid maxillary expansion, mandibular advancement, and lingual tonsillar removal.[4, 29, 101]

1.1.8 Upper airway imaging modalities

Visualization and calculation of the airway dimensions are of interest because airway obstructions increase airway resistance that may contribute to abnormal craniofacial growth. In addition to diagnosing obstruction, airway imaging provides an objective tool to measure changes in airway after therapy or correlate airway with craniofacial growth. The preferred radiological technique to evaluate the upper airway in children with structural or functional abnormalities is determined by the clinical condition of the patient, severity and complexity of the disorder, the available diagnostic expertise and resources.

Imaging of the upper airway and associated dentofacial structures has traditionally employed lateral cephalometric radiography. Characteristic differences have been described in skeletal, oral, and pharyngeal dimensions between OSA subjects and their normal peers. Cephalometry is informative and readily available however possess the limitations of any two-dimensional (2D) radiographic procedure: magnification, superimposition of surrounding structure, and changes which occur in the medio-lateral dimension cannot be visualized. With good to fair sensitivity (61-75%) and poor specificity (41-55%), lateral cephalograms are considered screening tools of adenoid hypertrophy that likely needs to be augmented with advanced three dimensional (3D) imaging in complex cases such as SDB population.[102, 103]

The airway extends from the tip of the nose to the superior aspect of the trachea and can be visualized on advanced imaging modalities such as magnetic resonance imaging (MRI), multi-detector computed tomography (MDCT), and cone beam CT (CBCT) scans which usually include the jaws, teeth, cranial base, spine, and facial soft tissues. This provides an opportunity to evaluate functional and developmental relationships between these structures. Of the three, MRI

is the most desirable as it has no ionizing radiation, provides information on the airway space and soft tissue definition of the muscles, fat, and lymphoid tissues forming and surrounding the airway. Certain ultra-fast MRI sequences can provide dynamic imaging of the airway. However, MRI is not readily accessible to dentists and static image sequences take a long time to complete. While MDCT provides high-resolution bone anatomy and soft tissue information by means of its thin-collimation, fan-shaped beam, it subjects the patients to high amounts of radiation (around 860 microSv for 12 cm high field of view)[104] and is not accessible to dentists. On the other hand, CBCT is readily available to dentists and provides 10 times less ionizing radiation, compared to MDCT, by means of its large, cone-shaped x-ray beam.[104] Cone beam CT was found reliable in evaluating adenoid size compared to nasoendoscopy, measuring the volume of an air space surrounded by soft tissue compared to MDCT, and allows precise measurements due to its small isotropic pixels.[105-107] Caveats to CBCT include the suboptimal resolution due to scatter radiation, lack of soft tissue delineation, and harmful ionizing radiation if the protocol is not adequately customized to fit the needs of each patient.

Of note, MDCT and MRI are acquired while the patient is in supine position thus allowing imaging subjects awake or asleep. Most CBCT units, on the other hand, acquire images in the seated position. Studies revealed that airway dimensions reduce at supine vs. seated position due to backward-downward position of the tongue, soft palate, and hyoid bone by means of gravity.[108-111] However, transitioning from awake to sleep introduces additional neuro-muscular factors that further affect airway dimensions through different stages of sleep or as subjects change between different postures during sleep; right or left supine, semi-supine, or prone.[7, 41, 112-115]

1.1.9 Upper airway imaging: methods of analysis

The literature contains studies analyzing different parts of the upper airway and utilizing different methods of analysis. The analysis is either static (linear, surface area, cross-sectional area, or volume) or dynamic (assess airflow by means of computational fluid dynamics). Computational fluid dynamics (CFD) is a computerized method of air flow analysis in which numerical methods and algorithms are used to simulate air or fluid flows. This technique is becoming more prominent because it allows more detailed information about air flow with outcome measures such as resistance, velocity, changes in pressure, and turbulence.[116] However, CFD is complex, computationally demanding, and time consuming due to the complex shape of the upper airway.[117]

Most recent analyses require a 3D model of the upper airway reconstructed from 3D imaging modality (MDCT, CBCT, or MRI) and in order to depict cross sections and volumes in a 3D analysis, the segmentation technique plays an important role.[118] Segmentation is the extraction of structural information of particular interest from surrounding images for visualization or characterization of anatomy or pathology by means of 3D reconstruction.[119] This process can be carried out manually, automatically or semi-automatically. Manual segmentation requires the operator to manually trace the boundaries or adjust pixel grey-threshold of the area of interest. As such, it requires long time, however it provides accurate 3D rendering of the airway. Automatic segmentation is offered usually by commercial software products and is time efficient however not as accurate as manual segmentation as they tend to "combine" the grey-threshold levels of the entire area of interest rather than customize it depending on location.

The most common applications of 3D analysis are: comparing airway dimensions between SDB subjects and their controls, assess airway changes after therapy, or associate airway parameters with craniofacial growth.

Upper airway imaging: SDB vs. control

Recent studies have shown that anatomical properties determined from CT, MRI, or CBCT images do correlate well with the severity of the OSA by different means of measurements. Barkdull and co-workers examined cross-sectional MDCT images of patients with OSA and found that a smaller retro-lingual airway correlated with the severity of OSA as measured by AHI.[120] MDCT and CBCT studies comparing OSA subjects with controls revealed that the presence of OSA was associated with an increase in airway length, smaller minimum cross-sectional area, and elliptically shaped airways.[121-123] Several MRI studies revealed that subjects with OSA had larger soft tissues (adenoids, tonsils, and soft palate)[124-127], narrow retro-palatal airway space[19, 126, 127], smaller mandibular volume[126], and presented with larger fluctuations in airway in tidal breathing[11]. Using fast MRI, few studies analyzed dynamic motion of the upper airway of OSA subjects and revealed transverse distention, pharyngeal collapse and narrowing during tidal breathing.[10, 127-130]

Applying CFD on 3D models generated from MRI[131] or MDCT[132, 133] showed that flow resistance in the pharynx and pressure drop at adenoid and tonsils were higher in OSA subjects, compared to their controls, and correlated with AHI.

Upper airway imaging: Assess treatment outcomes

Using MRI, few studies identified lingual tonsil hypertrophy as a reason for residual OSA[127, 134] and significant residual adenoid tissue and volume increase in the tongue and soft palate after AT in obese OSA children.[135]

In MDCT or CBCT studies, maxillary or maxillary-mandibular (MMA) advancement increased the minimum cross-sectional area and pharyngeal airway volume.[136-140] Conversely, a significant decrease was noted in volumes of oropharyngeal and hypopharyngeal airways after surgical mandibular set-back and in oropharyngeal airway after bi-maxillary surgery, in skeletal class III subjects.[141-146] While RME was shown to increase the nasal or pharyngeal airway in a few studies[147-150], there were no changes in the oro-pharyngeal airway in others.[151-157] Using CBCT, volume increase in the oropharynx was documented after Twin Block[158], Crossbow (XBow)[159], and Herbst[160] appliance therapies.

Applying CFD on 3D models generated from MDCT[161], CBCT[117], or MRI[162], air turbulence and pressure gradient reduced along the pharyngeal airway and strongly correlated with reduction in AHI after MMA and AT. Nasal ventilation improved by RME due to reduction in nasal resistance and negative pressure in pharynx, and reduction in velocity variations by means of CFD applied on CBCT-reconstructed airway models.[148, 163, 164]

Upper airway imaging: Association with craniofacial growth

Correlation between airway measures in CBCT and skeletal patterns is contradictory. Few studies found that volume and several cross-sectional areas in at least one part of the

pharyngeal airway were different amongst different skeletal patterns[165-170], with pharyngeal airway being largest in the skeletal Class III (mandibular prognathism) or low mandibular angle, followed by Class I, and then Class II (mandibular retrognathism) or high mandibular angle. Others found no difference in airway measures in different skeletal malocclusion patterns.[118, 171, 172]

1.2 Statement of the problem

Although adenotonsillectomy is the most common and first line of treatment for pediatric SDB, only one study[135] (MRI) measured upper airway changes after AT.

It is clearly evident that the majority of CBCT studies on upper airway either used manual or automatic segmentation of the pharynx. Few attempts were made to create automatic segmentation algorithms, however these were developed or tested only for the pharyngeal airway or required further tests to increase presicion.[173, 174] As interest in airway imaging using CBCT grew, a large influx of new commercial software programs or applications specific for airway analysis is noted. This is evident by the increasing amount of studies introducing, testing, or validating automatic commercial software products. However, few points are worth discussing:

- In an imaging modality with low signal to noise ratio, i.e. CBCT, reliability and accuracy of automatic segmentation techniques or commercial software products are important. If such programs were tested and deemed reliable or accurate, it is possibly as a result of using geometric phantoms consisting of cylinder or simple shapes as the "reference or gold standard".[175, 176] A more representable reference would be manual segmentation of true upper airway rather than a cylindrical phantom. Similarly, it is expected that automatic segmentation would closely represent that of manual segmentation, thus over-representing its reliability. For example, when the nasal cavity was included in testing automatic segmentation of a common software (Dolphin®), the upper airway volume differed by 42% against manual segmentation; a result deemed unacceptable.[177] Including the nasal cavity in validation of segmentation methods is more evident in the otolaryngology literature.[178-181] Semi-automatic segmentation of the nose and paranasal

sinuses reduced segmentation time by 78.1% however even the reduction to 3.5 hours was still considered not-practical clinically nor for research purposes.[181]

- There are multiple and inconsistent measurements of the upper airway that may or may not correlate with each other. Upper airway analysis in CBCT cannot be accurately expressed by single linear measurements and volume alone does not depict the morphology of the airway.[182] Since the upper airway is a complex geometry, its assessment should reflect size and shape parameters; conventional measures such as linear, area, and volume may fall short on the latter.
- When longitudinal CBCT analysis of the upper airway is carried out, most studies did not take into account changes in patient head position at the time of scan. Furthermore, sub-dividing the pharyngeal airways into different segments appears erroneous, inconsistent, and relies on unstable or unclear soft tissue landmarks. This, in turn, will impact the location and size of the linear, area, and volume measurements selected to analyze the upper airway.

In a pediatric population presenting with craniofacial disproportion and SDB symptoms, can we analyse their nasal and pharyngeal airways before and after adenoidectomy or tonsillectomy with meaningful measures, based on accurate CBCT models and reliable superimposition technique?

1.3 Objectives and Hypotheses

Objective 1: To assess reliability and accuracy of CBCT auto/semi-automatic segmentation technique specific for the upper airway.

> **Hypothesis 1 (H_0):** There is no significant difference in the dimensions of 3D upper airway models generated semi-automatically compared to manual segmentation "the reference".

Objective 2: To test reliability of registration technique based on anatomical landmarks specific for longitudinal upper airway CBCT images.

> **Hypothesis 2 (H_a):** Landmark-based registration technique is reliable method for upper airway CBCT superimposition.

Objective 3: To explore new parameters that take into account localized characteristics of the 3D upper airway.

> **Hypothesis 3 (H_a):** New parameters measuring the 3D upper airway correlate with and complement conventional/global measures.

Objective 4: To apply the tools in aforementioned objectives to assess adenoidectomy or tonsillectomy outcomes based on 3D upper airway models against quality of life measure OSA-18, in a pediatric population with jaw disproportions and sleep disordered breathing symptoms.

> **Hypothesis 4 (H_a):** 3D upper airway models, landmark-based registration, and new methods of analysis provide objective tool to measure surgical outcome and correlates with OSA-18 measures.

1.4 General Scope of Dissertation

The thesis is presented in seven chapters. This chapter, **Chapter 1**, represents a general introduction that reviews pertinent literature, states relevant problems identified, lists specific objectives and hypotheses to be tested, and finally the thesis scope is presented.

In **Chapter 2**, two systematic reviews are presented. Both reviews highlight the lack of optimized CBCT protocol for airway imaging, questionable validity and reliability of automatically-generated 3D airway models from CBCT, debatable sufficiency of linear, area, and volumetric measures to describe the airway, lack of clinical cross validation to determine if CBCT airway dimensional changes are suitable for assessment of treatment outcome, and deficiency of CBCT studies to assess pediatric SDB treatment outcomes. Although several upper airway CBCT studies have emerged since the two reviews, most if not all the discussed shortcomings still apply.

Chapter 3 describes two pilots. The first aimed to enhance the inherent low signal to noise ratio of the CBCT and consequently improve the delineation of airway boundaries and segmentation accuracy. This was completed by testing several application methods of topical radiograph contrast to the upper airway however different methods did not distribute throughout the upper airway. The second pilot tests a possible method to better analyze the upper airway using the center skeleton (or medial axis) of the 3D model and although was promising, two major issues subsequently became evident: 1) when the available software generates "skeletons or centerlines" based on two CBCT images, for the same airway, taken 6 months apart with no airway surgery applied, they are drastically different. 2) To overcome this, a new algorithm to

generate the "centerline" needs to be developed. Efforts to do so have proven to require extensive computational testing that cannot parallel the time frame of this dissertation. Accordingly, both pilots were not used in subsequent projects.

In **Chapter 4,** a 6-point landmark registration technique is introduced, validated, and its impact on upper airway is detailed by point-based analysis. This project also elucidates the impact of neck flexion and tongue position on upper airway to protocol CBCT imaging in following chapters.

Chapter 5, comprises three projects. The first ensures the reliability of manual tracing of the nasal and pharyngeal airways by the principal investigator (i.e. the PhD student) as manual segmentation will be considered the reference to test the semi-automatic segmentation program in the following projects. The second and third projects introduce the semi-automatic segmentation algorithm and tests its reliability, validity, and time efficiency, as well as utilizes the new point-based analysis of the 3D models.

Chapter 6 combines the segmentation program, registration technique, and point-based analyses developed in chapters 4 and 5 to generate and superimpose 3D airway models in 10 children with jaw disproportion and SDB symptoms before and after adenoidectomy or tonsillectomy. The changes in airway parameters are tested against changes in quality of life by means of OSA-18 survey.

Finally, **Chapter 7** provides general discussion, limitations and suggestions for future studies, and conclusions to further enhance the tools of CBCT upper airway analysis.

1.5 References

1. Jackman AR, Biggs SN, Walter LM, et al. Sleep-disordered breathing in preschool children is associated with behavioral, but not cognitive, impairments. *Sleep Med.* 2012:13:621-631.

2. Punjabi NM. The epidemiology of adult obstructive sleep apnea. *Proceedings of the American Thoracic Society.* 2008;5:136-143.

3. Lumeng JC, Chervin RD. Epidemiology of pediatric obstructive sleep apnea. *Proceedings of the American Thoracic Society.* 2008;5:242-252.

4. Katz ES, D'Ambrosio CM. Pathophysiology of pediatric obstructive sleep apnea. *Proceedings of the American Thoracic Society.* 2008;5:253-262.

5. Acosta P, Varon J. The upper airway resistance syndrome: Fact or fiction? *Current Respiratory Medicine Reviews.* 2008;4:1.

6. Katz ES, Marcus CL, White DP. Influence of airway pressure on genioglossus activity during sleep in normal children. *American Journal of Respiratory and Critical Care Medicine.* 2006;173:902-909.

7. Dempsey JA, Veasey SC, Morgan BJ, O'Donnell CP. Pathophysiology of sleep apnea. *Physiol Rev.* 2010;90:47-112.

8. Guilleminault C, Ji HL, Chan A. Pediatric obstructive sleep apnea syndrome. *Archives of Pediatrics and Adolescent Medicine.* 2005;159:775-785.

9. Guilleminault C, Li K, Quo S, Inouye RN. A prospective study on the surgical outcomes of children with sleep-disordered breathing. *Sleep.* 2004;27:95-100.

10. Donnelly LF, Surdulescu V, Chini BA, Casper KA, Poe SA, Amin RS. Upper airway motion depicted at cine MR imaging performed during sleep: Comparison between young patients with and those without obstructive sleep apnea. *Radiology.* 2003;227:239-245.

11. Arens R, Sin S, McDonough JM, et al. Changes in upper airway size during tidal breathing in children with obstructive sleep apnea syndrome. *American Journal of Respiratory and Critical Care Medicine.* 2005;171:1298-1304.

12. Isono S, Shimada A, Utsugi M, Konno A, Nishino T. Comparison of static mechanical properties of the passive pharynx between normal children and children with sleep-disordered breathing. *American Journal of Respiratory and Critical Care Medicine.* 1998;157:1204-1212.

13. Goldbart AD, Goldman JL, Li RC, Brittian KR, Tauman R, Gozal D. Differential expression of cysteinyl leukotriene receptors 1 and 2 in tonsils of children with obstructive sleep apnea syndrome or recurrent infection. *Chest.* 2004;126:13-18.

14. Kheirandish L, Goldbart AD, Gozal D. Intranasal steroids and oral leukotriene modifier therapy in residual sleep-disordered breathing after tonsillectomy and adenoidectomy in children. *Pediatrics.* 2006;117:e61-e66.

15. Goldbart AD, Goldman JL, Veling MC, Gozal D. Leukotriene modifier therapy for mild sleep-disordered breathing in children. *American Journal of Respiratory and Critical Care Medicine.* 2005;172:364-370.

16. Linder Aronson S, Leighton BC. A longitudinal study of the development of the posterior nasopharyngeal wall between 3 and 16 years of age. *Eur J Orthod.* 1983;5:47-58.

17. Vogler RC, Wippold II FJ, Pilgram TK. Age-specific size of the normal adenoid pad on magnetic resonance imaging. *Clin Otolaryngol.* 2000;25:392-395.

18. Arens R, McDonough JM, Costarino AT, et al. Magnetic resonance imaging of the upper airway structure of children with obstructive sleep apnea syndrome. *American Journal of Respiratory and Critical Care Medicine.* 2001;164:698-703.

19. Fregosi RF, Quan SF, Kaemingk KL, et al. Sleep-disordered breathing, pharyngeal size and soft tissue anatomy in children. *J Appl Physiol.* 2003;95:2030-2038.

20. Stallman JS, Lobo JN, Som PM. The incidence of concha bullosa and its relationship to nasal septal deviation and paranasal sinus disease. *Am J Neuroradiol.* 2004;25:1613-1618.

21. Kim YM, Rha K-, Weissman JD, Hwang PH, Most SP. Correlation of asymmetric facial growth with deviated nasal septum. *Laryngoscope.* 2011;121:1144-1148.

22. Miller AJ, Vargervik K, Chierici G. Experimentally induced neuromuscular changes during and after nasal airway obstruction. *Am J Orthod.* 1984;85:385-392.

23. Vargervik K, Harvold EP. Experiments on the interaction between orofacial function and morphology. *Ear, Nose and Throat Journal.* 1987;66:26-39.

24. Vargervik K, Miller AJ, Chierici G, Harvold E, Tomer BS. Morphologic response to changes in neuromuscular patterns experimentally induced by altered modes of respiration. *Am J Orthod.* 1984;85:115-124.

25. Harvold EP, Tomer BS, Vargervik K, Chierici G. Primate experiments on oral respiration. *Am J Orthod.* 1981;79:359-372.

26. Rubin RM. Effects of nasal airway obstruction on facial growth. *Ear, Nose and Throat Journal.* 1987;66:44-53.

27. Huang Y-, Guilleminault C. Pediatric obstructive sleep apnea and the critical role of oral-facial growth: Evidences. *Frontiers in Neurology.* 2013;3 JAN.

28. Bergeson PS, Shaw JC. Are infants really obligatory nasal breathers? *Clin Pediatr.* 2001;40:567-569.

29. Katz ES, D'Ambrosio CM. Pediatric obstructive sleep apnea syndrome. *Clin Chest Med.* 2010;31:221-234.

30. Huynh NT, Morton PD, Rompré PH, Papadakis A, Remise C. Associations between sleep-disordered breathing symptoms and facial and dental morphometry, assessed with screening examinations. *American Journal of Orthodontics and Dentofacial Orthopedics.* 2011;140:762-770.

31. Kim JH, Guilleminault C. The nasomaxillary complex, the mandible, and sleep-disordered breathing. *Sleep and Breathing.* 2011;15:185-193.

32. Zettergren-Wijk L, Forsberg C-, Linder-Aronson S. Changes in dentofacial morphology after adeno-/tonsillectomy in young children with obstructive sleep apnoea - A 5-year follow-up study. *Eur J Orthod.* 2006;28:319-326.

33. Linder-Aronson S. Adenoids. their effect on mode of breathing and nasal airflow and their relationship to characteristics of the facial skeleton and the denition. A biometric, rhino-manometric and cephalometro-radiographic study on children with and without adenoids. *Acta Oto-Laryngologica, Supplement.* 1970;265:1-132.

34. Solow B, Siersbæk-Nielsen S, Greve E. Airway adequacy, head posture, and craniofacial morphology. *Am J Orthod.* 1984;86:214-223.

35. Macari AT, Bitar MA, Ghafari JG. New insights on age-related association between nasopharyngeal airway clearance and facial morphology. *Orthodontics and Craniofacial Research.* 2012;15:188-197.

36. Souki BQ, Pimenta GB, Franco LP, Becker HMG, Pinto JA. Changes in vertical dentofacial morphology after adeno-/tonsillectomy during deciduous and mixed dentitions mouth breathing children-1 year follow-up study. *Int J Pediatr Otorhinolaryngol.* 2010;74:626-632.

37. Fung E, Cave D, Witmans M, Gan K, El-Hakim H. Postoperative respiratory complications and recovery in obese children following adenotonsillectomy for sleep-disordered breathing: A case-control study. *Otolaryngology - Head and Neck Surgery.* 2010;142:898-905.

38. Tait AR, Voepel-Lewis T, Burke C, Kostrzewa A, Lewis I. Incidence and risk factors for perioperative adverse respiratory events in children who are obese. *Anesthesiology.* 2008;108:375-380.

39. Ye J, Liu H, Zhang G, Huang Z, Huang P, Li Y. Postoperative respiratory complications of adenotonsillectomy for obstructive sleep apnea syndrome in older children: Prevalence, risk factors, and impact on clinical outcome. *Journal of Otolaryngology - Head and Neck Surgery.* 2009;38:49-58.

40. Witmans M, Young R. Update on pediatric sleep-disordered breathing. *Pediatr Clin North Am.* 2011;58:571-589.

41. Dayyat E, Maarafeya MMA, Capdevila OS, Kheirandish-Gozal L, Montgomery-Downs HE, Gozal D. Nocturnal body position in sleeping children with and without obstructive sleep apnea. *Pediatr Pulmonol.* 2007;42:374-379.

42. Litman RS, Wake N, Chan L-L, et al. Effect of lateral positioning on upper airway size and morphology in sedated children. *Anesthesiology.* 2005;103:484-488.

43. Jung H, Choung R, Talley N. Gastroesophageal reflux disease and sleep disorders: Evidence for a causal link and therapeutic implications.
. *Journal of Neurogastroenterology and Motility.* 2010;16:22-29. doi:doi:10.5056/jnm.2010.16.1.22.

44. Sinha D, Guilleminault C. Sleep disordered breathing in children. *Indian J Med Res.* 2010;131:311-320.

45. Flores-Mir C, Korayem M, Heo G, Witmans M, Major MP, Major PW. Craniofacial morphological characteristics in children with obstructive sleep apnea syndrome: A systematic review and meta-analysis. *J Am Dent Assoc.* 2013;144:269-277.

46. Katyal V, Pamula Y, Martin AJ, Daynes CN, Kennedy JD, Sampson WJ. Craniofacial and upper airway morphology in pediatric sleep-disordered breathing: Systematic review and meta-analysis. *American Journal of Orthodontics and Dentofacial Orthopedics.* 2013;143:20-30.e3.

47. Flemons WW, Douglas NJ, Kuna ST, Rodenstein DO, Wheatley J. Access to diagnosis and treatment of patients with suspected sleep apnea. *American Journal of Respiratory and Critical Care Medicine.* 2004;169:668-672.

48. Alonso-Álvarez ML, Terán-Santos J, Ordax Carbajo E, et al. Reliability of home respiratory polygraphy for the diagnosis of sleep apnea in children. *Chest.* 2015;147:1020-1028.

49. Poels PJP, Schilder AGM, Van Den Berg S, Hoes AW, Joosten KFM. Evaluation of a new device for home cardiorespiratory recording in children. *Archives of Otolaryngology - Head and Neck Surgery.* 2003;129:1281-1284.

50. Certal V, Camacho M, Winck JC, Capasso R, Azevedo I, Costa-Pereira A. Unattended sleep studies in pediatric OSA: A systematic review and meta-analysis. *Laryngoscope.* 2015;125:255-262.

51. Brouillette RT, Morielli A, Leimanis A, Waters KA, Luciano R, Ducharme FM. Nocturnal pulse oximetry as an abbreviated testing modality for pediatric obstructive sleep apnea. *Pediatrics.* 2000;105:405-412.

52. Nixon GM, Kermack AS, Davis GM, Manoukian JJ, Brown KA, Brouillette RT. Planning adenotonsillectomy in children with obstructive sleep apnea: The role of overnight oximetry. *Pediatrics.* 2004;113:e19-25.

53. Kirk VG, Bohn SG, Flemons WW, Remmers JE. Comparison of home oximetry monitoring with laboratory polysomnography in children. *Chest.* 2003;124:1702-1708.

54. Parikh SR, Coronel M, Lee JJ, Brown SM. Validation of a new grading system for endoscopic examination of adenoid hypertrophy. *Otolaryngology - Head and Neck Surgery.* 2006;135:684-687.

55. Strauss RA, Burgoyne CC. Diagnostic imaging and sleep medicine. *Dent Clin North Am.* 2008;52:891-915.

56. Shigeta Y, Ogawa T, Venturin J, Nguyen M, Clark GT, Enciso R. Gender- and age-based differences in computerized tomographic measurements of the orophaynx. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontology.* 2008;106:563-570.

57. De Luca Canto G, Singh V, Major MP, et al. Diagnostic capability of questionnaires and clinical examinations to assess sleep-disordered breathing in children: A systematic review and meta-analysis. *J Am Dent Assoc.* 2014;145:165-178.

58. Chervin RD, Hedger K, Dillon JE, Pituch KJ. Pediatric sleep questionnaire (PSQ): Validity and reliability of scales for sleep-disordered breathing, snoring, sleepiness, and behavioral problems. *Sleep Med.* 2000;1:21-32.

59. Franco Jr. RA, Rosenfeld RM, Rao M. Quality of life for children with obstructive sleep apnea. *Otolaryngology - Head and Neck Surgery.* 2000;123:9-16.

60. Yang Y, Xu Z, Chen M, Zhang Y. [Exploration of screening scores for pediatric obstructive sleep apnea hypopnea syndrome]. *Lin chuang er bi yan hou tou jing wai ke za zhi = Journal of clinical otorhinolaryngology, head, and neck surgery.* 2012;26:680-683.

61. Goldstein NA, Stefanov DG, Graw-Panzer KD, et al. Validation of a clinical assessment score for pediatric sleep-disordered breathing. *Laryngoscope.* 2012;122:2096-2104.

62. Mitchell RB, Kelly J. Quality of life after adenotonsillectomy for SDB in children. *Otolaryngology - Head and Neck Surgery.* 2005;133:569-572.

63. Constantin E, Tewfik TL, Brouillette RT. Can the OSA-18 quality-of-life questionnaire detect obstructive sleep apnea in children? *Pediatrics.* 2010;125:e162-e168.

64. Borgström A, Nerfeldt P, Friberg D. Questionnaire OSA-18 has poor validity compared to polysomnography in pediatric obstructive sleep apnea. *Int J Pediatr Otorhinolaryngol.* 2013;77:1864-1868.

65. Friedman M, Samuelson CG, Hamilton C, et al. Modified adenotonsillectomy to improve cure rates for pediatric obstructive sleep apnea: A randomized controlled trial. *Otolaryngology - Head and Neck Surgery (United States).* 2012;147:132-138.

66. Tripuraneni M, Paruthi S, Armbrecht ES, Mitchell RB. Obstructive sleep apnea in children. *Laryngoscope.* 2013;123:1289-1293.

67. Ericsson E, Lundeborg I, Hultcrantz E. Child behavior and quality of life before and after tonsillotomy versus tonsillectomy. *Int J Pediatr Otorhinolaryngol.* 2009;73:1254-1262.

68. Mitchell RB. Adenotonsillectomy for obstructive sleep apnea in children: Outcome evaluated by pre- and postoperative polysomnography. *Laryngoscope.* 2007;117:1844-1854.

69. Mitchell RB, Garetz S, Moore RH, et al. The use of clinical parameters to predict obstructive sleep apnea syndrome severity in children: The childhood adenotonsillectomy (CHAT) study randomized clinical trial. *JAMA Otolaryngology - Head and Neck Surgery.* 2015;141:130-136.

70. Peña-Zarza JA, Osona-Rodriguez De Torres B, Gil-Sanchez JA, Figuerola-Mulet J. Utility of the pediatric sleep questionnaire and pulse oximetry as screening tools in pediatric patients with suspected obstructive sleep apnea syndrome. . *Sleep Disorders.* 2012;Article ID 819035:6 pages. doi:http://dx.doi.org/10.1155/2012/819035.

71. Chervin RD, Weatherly RA, Ruzicka DL, et al. Subjective sleepiness and polysomnographic correlates in children scheduled for adenotonsillectomy vs other surgical care. *Sleep.* 2006;29:495-503.

72. Garetz SL, Mitchell RB, Parker PD, et al. Quality of life and obstructive sleep apnea symptoms after pediatric adenotonsillectomy. *Pediatrics.* 2015;135:e477-e486.

73. Marcus CL, Rosen G, Davidson Ward SL, et al. Adherence to and effectiveness of positive airway pressure therapy in children with obstructive sleep apnea. *Pediatrics.* 2006;117:e442-e451.

74. Korayem MM, Witmans M, MacLean J, et al. Craniofacial morphology in pediatric patients with persistent obstructive sleep apnea with or without positive airway pressure therapy: A cross-sectional cephalometric comparison with controls. *American Journal of Orthodontics and Dentofacial Orthopedics.* 2013;144:78-85.

75. 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 and Breathing.* 2011;15:179-184.

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

77. Guilleminault C, Monteyrol P-, Huynh NT, Pirelli P, Quo S, Li K. Adeno-tonsillectomy and rapid maxillary distraction in pre-pubertal children, a pilot study. *Sleep and Breathing.* 2011;15:173-177.

78. Guilleminault C, Quo S, Huynh NT, Li K. Orthodontic expansion treatment and adenotonsillectomy in the treatment of obstructive sleep apnea in prepubertal children (retraction in: Sleep (2010) 33:1 (8)). *Sleep.* 2008;31:953-957.

79. Guilleminault C, Huang Y-, Quo S, Monteyrol P-, Lin C-. Teenage sleep-disordered breathing: Recurrence of syndrome. *Sleep Med.* 2013;14:37-44.

80. Cistulli PA, Palmisano RG, Poole MD. Treatment of obstructive sleep apnea syndrome by rapid maxillary expansion. *Sleep.* 1998;21:831-835.

81. Palmisano RG, Wilcox I, Sullivan CE, Cistulli PA. Treatment of snoring and obstructive sleep apnoea by rapid maxillary expansion. *Aust N Z J Med.* 1996;26:428-429.

82. Miano S, Rizzoli A, Evangelisti M, et al. NREM sleep instability changes following rapid maxillary expansion in children with obstructive apnea sleep syndrome. *Sleep Med.* 2009;10:471-478.

83. Villa MP, Bernkopf E, Pagani J, Broia V, Montesano M, Ronchetti R. Randomized controlled study of an oral jaw-positioning appliance for the treatment of obstructive sleep apnea in children with malocclusion. *American Journal of Respiratory and Critical Care Medicine.* 2002;165:123-127.

84. Özbek MM, Toygar Memikoglu TU, Gögen H, Lowe AA, Baspinar E. Oropharyngeal airway dimensions and functional-orthopedic treatment in skeletal class II cases. *Angle Orthod.* 1998;68:327-336.

85. Kapust AJ, Sinclair PM, Turley PK. Cephalometric effects of face mask/expansion therapy in class III children: A comparison of three age groups. *Am J Orthod Dentofacial Orthop.* 1998;113:204-212.

86. Hiyama S, Suda N, Ishii-Suzuki M, et al. Effects of maxillary protraction on craniofacial structures and upper-airway dimension. *Angle Orthod.* 2002;72:43-47.

87. Kilinç AS, Arslan SG, Kama JD, Özer T, Dari O. Effects on the sagittal pharyngeal dimensions of protraction and rapid palatal expansion in class III malocclusion subjects. *Eur J Orthod.* 2008;30:61-66.

88. Oktay H, Ulukaya E. Maxillary protraction appliance effect on the size of the upper airway passage. *Angle Orthod.* 2008;78:209-214.

89. Kaygsz E, Tuncer BB, Yüksel S, Tuncer C, Yildiz C. Effects of maxillary protraction and fixed appliance therapy on the pharyngeal airway. *Angle Orthod.* 2009;79:660-667.

90. Sayinsu K, Isik F, Arun T. Sagittal airway dimensions following maxillary protraction: A pilot study. *Eur J Orthod.* 2006;28:184-189.

91. Conley RS. Evidence for dental and dental specialty treatment of obstructive sleep apnoea. part 1: The adult OSA patient and part 2: The paediatric and adolescent patient. *J Oral Rehabil.* 2011;38:136-156.

92. Schechter MS. Technical report: Diagnosis and management of childhood obstructive sleep apnea syndrome. *Pediatrics.* 2002;109.

93. Marcus CL, Moore RH, Rosen CL, et al. A randomized trial of adenotonsillectomy for childhood sleep apnea. *N Engl J Med.* 2013;368:2366-2376.

94. Tauman R, Gulliver TE, Krishna J, et al. Persistence of obstructive sleep apnea syndrome in children after adenotonsillectomy. *J Pediatr.* 2006;149:803-808.

95. Guilleminault C, Huang Y-, Glamann C, Li K, Chan A. Adenotonsillectomy and obstructive sleep apnea in children: A prospective survey. *Otolaryngology - Head and Neck Surgery.* 2007;136:169-175.

96. Friedman M, Wilson M, Lin H-, Chang H-. Updated systematic review of tonsillectomy and adenoidectomy for treatment of pediatric obstructive sleep apnea/hypopnea syndrome. *Otolaryngology - Head and Neck Surgery.* 2009;140:800-808.

97. Costa DJ, Mitchell R. Adenotonsillectomy for obstructive sleep apnea in obese children: A meta-analysis. *Otolaryngology - Head and Neck Surgery.* 2009;140:455-460.

98. Bhattacharjee R, Kheirandish-Gozal L, Spruyt K, et al. Adenotonsillectomy outcomes in treatment of obstructive sleep apnea in children: A multicenter retrospective study. *American Journal of Respiratory and Critical Care Medicine.* 2010;182:676-683.

99. Morton S, Rosen C, Larkin E, Tishler P, Aylor J, Redline S. Predictors of sleep-disordered breathing in children with a history of tonsillectomy and/or adenoidectomy. *Sleep.* 2001;24:823-829.

100. Wasilewska J, Kaczmarski M, Debkowska K. Obstructive hypopnea and gastroesophageal reflux as factors associated with residual obstructive sleep apnea syndrome. *Int J Pediatr Otorhinolaryngol.* 2011;75:657-663.

101. Wasilewska J, Semeniuk J, Cudowska B, Klukowski M, Debkowska K, Kaczmarski M. Respiratory response to proton pump inhibitor treatment in children with obstructive sleep apnea syndrome and gastroesophageal reflux disease. *Sleep Med.* 2012;13:824-830.

102. Major MP, Flores-Mir C, Major PW. Assessment of lateral cephalometric diagnosis of adenoid hypertrophy and posterior upper airway obstruction: A systematic review. *American Journal of Orthodontics and Dentofacial Orthopedics.* 2006;130:700-708.

103. Major MP, Saltaji H, El-Hakim H, Witmans M, Major P, Flores-Mir C. The accuracy of diagnostic tests for adenoid hypertrophy : A systematic review. *J Am Dent Assoc.* 2014;145:247-254.

104. Ludlow JB, Ivanovic M. Comparative dosimetry of dental CBCT devices and 64-slice CT for oral and maxillofacial radiology. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontology.* 2008;106:930-938.

105. 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 Radiology.* 2008;37:245-251.

106. 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. *American Journal of Orthodontics and Dentofacial Orthopedics.* 2009;135:468-479.

107. Major MP, Witmans M, El-Hakim H, Major PW, Flores-Mir C. Agreement between cone-beam computed tomography and nasoendoscopy evaluations of adenoid hypertrophy. *American Journal of Orthodontics and Dentofacial Orthopedics.* 2014;146:451-459.

108. Camacho M, Capasso R, Schendel S. Airway changes in obstructive sleep apnoea patients associated with a supine versus an upright position examined using cone beam computed tomography. *J Laryngol Otol.* 2014.

109. Van Holsbeke CS, Verhulst SL, Vos WG, et al. Change in upper airway geometry between upright and supine position during tidal nasal breathing. *Journal of Aerosol Medicine and Pulmonary Drug Delivery.* 2014;27:51-57.

110. Sutthiprapaporn P, Tanimoto K, Ohtsuka M, Nagasaki T, Iida Y, Katsumata A. Positional changes of oropharyngeal structures due to gravity in the upright and supine positions. *Dentomaxillofacial Radiology.* 2008;37:130-136.

111. Battagel JM, Johal A, Smith A-, Kotecha B. Postural variation in oropharyngeal dimensions in subjects with sleep disordered breathing: A cephalometric study. *Eur J Orthod.* 2002;24:263-276.

112. Tsuiki S, Almeida FR, Bhalla PS, Lowe AA, Fleetham JA. Supine-dependent changes in upper airway size in awake obstructive sleep apnea patients. *Sleep and Breathing.* 2003;7:43-50.

113. Trudo FJ, Gefter WB, Welch KC, Gupta KB, Maislin G, Schwab RJ. State-related changes in upper airway caliber and surrounding soft- tissue structures in normal subjects. *American Journal of Respiratory and Critical Care Medicine.* 1998;158:1259-1270.

114. Tiotiu A, Mairesse O, Hoffmann G, Todea D, Noseda A. Body position and breathing abnormalities during sleep: A systematic study. *Pneumologia.* 2011;60:216-221.

115. Penzel T, Möller M, Becker HF, Knaack L, Peter J-. Effect of sleep position and sleep stage on the collapsibility of the upper airways in patients with sleep apnea. *Sleep.* 2001;24:90-95.

116. Van Holsbeke C, Vos W, Van Hoorenbeeck K, et al. Functional respiratory imaging as a tool to assess upper airway patency in children with obstructive sleep apnea. *Sleep Med.* 2013;14:433-439.

117. Huynh J, Kim D, McQuilling M. Pharyngeal airflow analysis in obstructive sleep apnea patients pre- and post-maxillomandibular advancement surgery. *J of fluids Eng.* 2009;131:091101-091111.

118. Di Carlo G, Polimeni A, Melsen B, Cattaneo PM. The relationship between upper airways and craniofacial morphology studied in 3D. A CBCT study. *Orthodontics and Craniofacial Research.* 2015;18:1-11.

119. Pham D, Xu C, Prince J. Current methods in medical image segmentation. *annu rev biomed eng.* 2000;02:315-37.

120. Barkdull GC, Kohl CA, Patel M, Davidson TM. Computed tomography imaging of patients with obstructive sleep apnea. *Laryngoscope.* 2008;118:1486-1492.

121. Abramson Z, Susarla S, August M, Troulis M, Kaban L. Three-dimensional computed tomographic analysis of airway anatomy in patients with obstructive sleep apnea. *Journal of Oral and Maxillofacial Surgery.* 2010;68:354-362.

122. Ogawa T, Enciso R, Memon A, Mah J, Clark G. Evaluation of 3D airway imaging of obstructive sleep apnea with cone-beam computed tomography. *Stud Health Technol Inform.* 2005;111:365-368.

123. Sato K, Shirakawa T, Sakata H, Asanuma S. Effectiveness of the analysis of craniofacial morphology and pharyngeal airway morphology in the treatment of children with obstructive sleep apnoea syndrome. *Dentomaxillofacial Radiology.* 2012;41:411-416.

124. Arens R, McDonough JM, Costarino AT, et al. Magnetic resonance imaging of the upper airway structure of children with obstructive sleep apnea syndrome. *American Journal of Respiratory and Critical Care Medicine.* 2001;164:698-703.

125. Arens R, Sin S, Nandalike K, et al. Upper airway structure and body fat composition in obese children with obstructive sleep apnea syndrome. *American Journal of Respiratory and Critical Care Medicine.* 2011;183:782-787.

126. Cappabianca S, Iaselli F, Negro A, et al. Magnetic resonance imaging in the evaluation of anatomical risk factors for pediatric obstructive sleep apnoea-hypopnoea: A pilot study. *Int J Pediatr Otorhinolaryngol.* 2013;77:69-75.

127. Donnelly LF, Shott SR, LaRose CR, Chini BA, Amin RS. Causes of persistent obstructive sleep apnea despite previous tonsillectomy and adenoidectomy in children with down syndrome as depicted on static and dynamic cine MRI. *Am J Roentgenol.* 2004;183:175-181.

128. Abbott MB, Donnelly LF, Dardzinski BJ, Poe SA, Chini BA, Amin RS. Obstructive sleep apnea: MR imaging volume segmentation analysis. *Radiology.* 2004;232:889-895.

129. Persak SC, Sin S, McDonough JM, Arens R, Wootton DM. Noninvasive estimation of pharyngeal airway resistance and compliance in children based on volume-gated dynamic MRI and computational fluid dynamics. *J Appl Physiol.* 2011;111:1819-1827.

130. Ikeda K, Ogura M, Oshima T, et al. Quantitative assessment of the pharyngeal airway by dynamic magnetic resonance imaging in obstructive sleep apnea syndrome. *Annals of Otology, Rhinology and Laryngology.* 2001;110:183-189.

131. Wootton DM, Luo H, Persak SC, et al. Computational fluid dynamics endpoints to characterize obstructive sleep apnea syndrome in children. *J Appl Physiol.* 2014;116:104-112.

132. Van Holsbeke C, De Backer J, Vos W, et al. Anatomical and functional changes in the upper airways of sleep apnea patients due to mandibular repositioning: A large scale study. *J Biomech.* 2011;44:442-449.

133. Vos W, De Backer J, Devolder A, et al. Correlation between severity of sleep apnea and upper airway morphology based on advanced anatomical and functional imaging. *J Biomech.* 2007;40:2207-2213.

134. Fricke BL, Donnelly LF, Shott SR, et al. Comparison of lingual tonsil size as depicted on MR imaging between children with obstructive sleep apnea despite previous tonsillectomy and adenoidectomy and normal controls. *Pediatr Radiol.* 2006;36:518-523.

135. Nandalike K, Shifteh K, Sin S, et al. Adenotonsillectomy in obese children with obstructive sleep apnea syndrome: Magnetic resonance imaging findings and considerations. *Sleep.* 2013;36:841-847.

136. Brunetto DP, Velasco L, Koerich L, Araújo MTDS. Prediction of 3-dimensional pharyngeal airway changes after orthognathic surgery: A preliminary study. *American Journal of Orthodontics and Dentofacial Orthopedics.* 2014;146:299-309.

137. De Souza Carvalho ACG, Magro Filho O, Garcia IR, Araujo PM, Nogueira RLM. Cephalometric and three-dimensional assessment of superior posterior airway space after maxillomandibular advancement. *Int J Oral Maxillofac Surg.* 2012;41:1102-1111.

138. Raffaini M, Pisani C. Clinical and cone-beam computed tomography evaluation of the three-dimensional increase in pharyngeal airway space following maxillo-mandibular rotation-advancement for class II-correction in patients without sleep apnoea (OSA). *Journal of Cranio-Maxillofacial Surgery.* 2013;41:552-557.

139. Butterfield KJ, Marks PLG, McLean L, Newton J. Pharyngeal airway morphology in healthy individuals and in obstructive sleep apnea patients treated with maxillomandibular advancement: A comparative study. *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology.* 2015;119:285-292.

140. Valladares-Neto J, Silva MAG, Bumann A, Paiva JB, Rino-Neto J. Effects of mandibular advancement surgery combined with minimal maxillary displacement on the volume and most restricted cross-sectional area of the pharyngeal airway. *Int J Oral Maxillofac Surg.* 2013;42:1437-1445.

141. Park S-, Kim Y-, Son W-, Hwang D-, Cho B-. Cone-beam computed tomography evaluation of short- and long-term airway change and stability after orthognathic surgery in patients with class III skeletal deformities: Bimaxillary surgery and mandibular setback surgery. *Int J Oral Maxillofac Surg.* 2012;41:87-93.

142. Shin J-, Kim M-, Park I-, Park Y-. A 2-year follow-up of changes after bimaxillary surgery in patients with mandibular prognathism: 3-dimensional analysis of pharyngeal airway volume and hyoid bone position. *Journal of Oral and Maxillofacial Surgery.* 2015;73:340.e1-340.e9.

143. Gokce SM, Gorgulu S, Gokce HS, Bengi AO, Karacayli U, Ors F. Evaluation of pharyngeal airway space changes after bimaxillary orthognathic surgery with a 3-dimensional simulation and modeling program. *American Journal of Orthodontics and Dentofacial Orthopedics.* 2014;146:477-492.

144. Hatab NA, Konstantinović VS, Mudrak JKH. Pharyngeal airway changes after mono- and bimaxillary surgery in skeletal class III patients: Cone-beam computed tomography evaluation. *Journal of Cranio-Maxillofacial Surgery.* 2014 Accessed 29 April 2015.

145. Li Y-, Liu J-, Zhao J-, Dai J, Wang L, Chen J-. Morphological changes in the pharyngeal airway of female skeletal class III patients following bimaxillary surgery: A cone beam computed tomography evaluation. *Int J Oral Maxillofac Surg.* 2014;43:862-867.

146. Sears CR, Miller AJ, Chang MK, Huang JC, Lee JS. Comparison of pharyngeal airway changes on plain radiography and cone-beam computed tomography after orthognathic surgery. *Journal of Oral and Maxillofacial Surgery.* 2011;69:e385-e394.

147. 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. *American Journal of Orthodontics and Dentofacial Orthopedics.* 2013;143:235-245.

148. Iwasaki T, Saitoh I, Takemoto Y, et al. Evaluation of upper airway obstruction in class II children with fluid-mechanical simulation. *American Journal of Orthodontics and Dentofacial Orthopedics.* 2011;139:e135-e145.

149. Bouserhal J, Bassil-Nassif N, Tauk A, Will L, Limme M. Three-dimensional changes of the naso-maxillary complex following rapid maxillary expansion. *Angle Orthod.* 2014;84:88-95.

150. Smith T, Ghoneima A, Stewart K, et al. Three-dimensional computed tomography analysis of airway volume changes after rapid maxillary expansion. *American Journal of Orthodontics and Dentofacial Orthopedics.* 2012;141:618-626.

151. 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. *American Journal of Orthodontics and Dentofacial Orthopedics.* 2010;137:S71-S78.

152. 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. *American Journal of Orthodontics and Dentofacial Orthopedics.* 2013;143:462-470.

153. 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;82:458-463.

154. El H, Palomo JM. Three-dimensional evaluation of upper airway following rapid maxillary expansion A CBCT study. *Angle Orthod.* 2014;84:265-273.

155. Zeng J, Gao X. A prospective CBCT study of upper airway changes after rapid maxillary expansion. *Int J Pediatr Otorhinolaryngol.* 2013;77:1805-1810.

156. Fastuca R, Zecca PA, Caprioglio A. Role of mandibular displacement and airway size in improving breathing after rapid maxillary expansion. *Progress in orthodontics.* 2014;15:40.

157. Kabalan O, Gordon J, Heo G, Lagravère MO. Nasal airway changes in bone-borne and tooth-borne rapid maxillary expansion treatments. *International Orthodontics.* 2015;13:1-15.

158. Li L, Liu H, Cheng H, et al. CBCT evaluation of the upper airway morphological changes in growing patients of class ii division 1 malocclusion with mandibular retrusion using twin block appliance: A comparative research. *PLoS ONE.* 2014;9: e94378.

159. Erbas B, Kocadereli I. Upper airway changes after xbow appliance therapy evaluated with cone beam computed tomography. *Angle Orthod.* 2014;84:693-700.

160. Iwasaki T, Takemoto Y, Inada, E, et al.. Three-dimensional cone-beam computed tomography analysis of enlargement of the pharyngeal airway by the herbst appliance. *American Journal of Orthodontics and Dentofacial Orthopedics.* 2014;146:776-785.

161. Yu C-, Hsiao H-, Lee L-, et al. Computational fluid dynamic study on obstructive sleep apnea syndrome treated with maxillomandibular advancement. *J Craniofac Surg.* 2009;20:426-430.

162. Luo H, Sin S, McDonough JM, Isasi CR, Arens R, Wootton DM. Computational fluid dynamics endpoints for assessment of adenotonsillectomy outcome in obese children with obstructive sleep apnea syndrome. *J Biomech.* 2014;47:2498-2503.

163. Iwasaki T, Saitoh I, Takemoto Y, et al. Improvement of nasal airway ventilation after rapid maxillary expansion evaluated with computational fluid dynamics. *American Journal of Orthodontics and Dentofacial Orthopedics.* 2012;141:269-278.

164. 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.

165. Abdelkarim A. A cone beam CT evaluation of oropharyngeal airway space and its relationship to mandibular position and dentocraniofacial morphology. *Journal of the World Federation of Orthodontists.* 2012;1:e55-e59.

166. El H, Palomo JM. Airway volume for different dentofacial skeletal patterns. *American Journal of Orthodontics and Dentofacial Orthopedics.* 2011;139:e511-e521.

167. Alves Jr. M, Franzotti ES, Baratieri C, Nunes LKF, Nojima LI, Ruellas ACO. Evaluation of pharyngeal airway space amongst different skeletal patterns. *Int J Oral Maxillofac Surg.* 2012;41:814-819.

168. Zheng ZH, Yamaguchi T, Kurihara A, Li HF, Maki K. Three-dimensional evaluation of upper airway in patients with different anteroposterior skeletal patterns. *Orthodontics and Craniofacial Research.* 2014;17:38-48.

169. Celikoglu M, Bayram M, Sekerci AE, Buyuk SK, Toy E. Comparison of pharyngeal airway volume among different vertical skeletal patterns: A cone-beam computed tomography study. *Angle Orthod.* 2014;84:782-787.

170. Claudino LV, Mattos CT, Ruellas ACDO, Sant Anna EF. Pharyngeal airway characterization in adolescents related to facial skeletal pattern: A preliminary study. *American Journal of Orthodontics and Dentofacial Orthopedics.* 2013;143:799-809.

171. Grauer D, Cevidanes LSH, Styner MA, Ackerman JL, Proffit WR. Pharyngeal airway volume and shape from cone-beam computed tomography: Relationship to facial morphology. *American Journal of Orthodontics and Dentofacial Orthopedics.* 2009;136:805-814.

172. Alves PVM, Zhao L, O'Gara M, Patel PK, Bolognese AM. Three-dimensional cephalometric study of upper airway space in skeletal class II and III healthy patients. *J Craniofac Surg.* 2008;19:1497-1507.

173. Shi H, Scarfe W, Farman A. Upper airway segmentation and dimensions estimation from cone-beam CT image datasets. *Int J CARS.* 2006;1:177-186.

174. Cheng I, Nilufar S, Flores-Mir C, Basu A. Airway segmentation and measurement in CT images. *Conference proceedings : ...Annual International Conference of the IEEE Engineering in Medicine and Biology Society.IEEE Engineering in Medicine and Biology Society.Conference.* 2007;2007:795-799.

175. Weissheimer A, Menezes LMD, Sameshima GT, Enciso R, Pham J, Grauer D. Imaging software accuracy for 3-dimensional analysis of the upper airway. *American Journal of Orthodontics and Dentofacial Orthopedics.* 2012;142:801-813.

176. Ghoneima A, Kula K. Accuracy and reliability of cone-beam computed tomography for airway volume analysis. *Eur J Orthod.* 2013;35:256-261.

177. de Water VR, Saridin JK, Bouw F, Murawska MM, Koudstaal MJ. Measuring upper airway volume: Accuracy and reliability of dolphin 3D software compared to manual segmentation in craniosynostosis patients. *Journal of Oral and Maxillofacial Surgery.* 2013:72:139-144.

178. Seo A, Chung SK, Lee J, Kim J-, Kim H. Semiautomatic segmentation of nasal airway based on collaborative environment. *Proceedings - 2010 International Symposium on Ubiquitous Virtual Reality, ISUVR 2010.* 2010:56-59.

179. Dastidar P, Heinonen T, Numminen J, Rautiainen M, Laasonen E. Semi-automatic segmentation of computed tomographic images in volumetric estimation of nasal airway. *European Archives of Oto-Rhino-Laryngology.* 1999;256:192-198.

180. Perchet D, Fetita C, Prêteux F. Three-dimensional reconstruction of upper airways from MDCT. *Proceedings of SPIE - The International Society for Optical Engineering.* 2005;5672:212-223.

181. Tingelhoff K, Moral AI, Kunkel ME, et al. Comparison between manual and semi-automatic segmentation of nasal cavity and paranasal sinuses from CT images. *Annual International Conference of the IEEE Engineering in Medicine and Biology - Proceedings.* 2007:5505-5508.

182. Lenza MG, de O. Lenza MM, Dalstra M, Melsen B, Cattaneo PM. An analysis of different approaches to the assessment of upper airway morphology: A CBCT study. *Orthodontics and Craniofacial Research.* 2010;13:96-105.

Chapter 2

Accuracy and use of CBCT generated 3D airway models: current evidence

2.1 Three-dimensional segmentation of the Upper Airway using CBCT: A systematic review

2.2 CBCT assessment of upper airway changes and treatment outcomes of obstructive sleep apnea: a systematic review

2.1 Three-dimensional segmentation of the Upper Airway using CBCT: A systematic review*

N. Alsufyani, C. Flores-Mir and P. Major

*Published in *Dentomaxillofacial Radiology* (2012) 41, 276–284.

2.1 Three-dimensional segmentation of the Upper Airway using CBCT: A systematic review

Abstract

Objectives: To systematically review the literature for studies using cone beam computed tomography (CBCT) to automatically or semi-automatically model the upper airway (including pharyngeal, nasal and paranasal airways) and to assess their validity and reliability. **Methods:** Several electronic databases (Medline, Medline In-Process & Other Non-Indexed Citations, all Evidence Based Medicine Reviews which includes the Cochrane Database, and Scopus) were searched. Abstracts that appeared to meet the initial selection criteria were selected by consensus. The original articles were then retrieved and their references were manually searched for potential articles that were missed during the electronic search. Final articles that met all the selection criteria were evaluated using a customized evaluation checklist. **Results:** Sixteen articles were finally selected. From these articles, five scored >50% based on their methodology. Although eight articles reported the reliability of the airway model generated, only three used Intra-class correlation (ICC). Two articles tested the accuracy/validity of airway models against the gold standard, manual segmentation, using volumetric measurements however neither used ICC. **Conclusions:** Only three articles properly tested the reliability of the 3D upper airway model generated from CBCT and only one article had sound methodology to test their accuracy/validity. The literature lacks proper scientific justification of a solid and optimized CBCT protocol for airway imaging. Due to the limited number of adequate studies, it is difficult to generate a strong conclusion regarding the current validity and reliability of CBCT-generated 3D models.

2.1.1 Introduction

Obstruction of the upper airway often alters normal breathing, which can have a significant impact on the normal development of craniofacial structures.[1,2] Narrow maxillary arch, cross bites, clockwise mandibular growth rotation, and mandibular retrognathia have been reported as being associated with chronic mouth breathing.[3] Many of these facial features have been also reported in subjects with sleep disordered breathing such as obstructive sleep apnea.[4, 5] Such abnormalities require prompt attention and an early diagnosis is imperative to ensure normal craniofacial development.[6]

Cone beam computed tomography (CBCT) has become available for oral and maxillofacial imaging. It has been suggested that CBCT provides an accurate, efficient and relatively less radiation modality, compared to multi-detector CT, for improved understanding of airway anatomy, pathology and upper airway mechanics.[7, 8]

Segmentation of the airway can be done manually or automatically. Manual segmentation seems to be the most accurate method and allows for the most operator control.[9] Accordingly, it is significantly time-consuming because it requires the operator to outline the airway boundaries on each slice and then transform the data into a 3D volume. Automatic segmentation, on the other hand, can drastically reduce segmentation time.[9]

Automatic or semi-automatic, three-dimensional segmentation of the upper airway can be very challenging especially in the complex anatomy of the nasal airway. It has been noted that several studies [6, 10-12] that assessed the use of CBCT scans to segment the airway did not provide validation of their proposed methods. Not only must a reliable but also valid model of the upper airway be reconstructed to accurately study the possible relationship between airway restriction and craniofacial growth using CBCT imaging.

The purpose of this study is therefore to systematically review the medical and dental literature for studies using CBCT to automatically or semi-automatically model the upper airway (including pharyngeal, nasal or paranasal airway) and to answer the following questions: Are 3D airway models automatically segmented from CBCT accurate and reliable? Can clinicians and surgeons use quantitative analysis based on these models?

2.1.2 Methods

A systematic search of multiple electronic databases was completed during the third week of May 2011. Databases searched were: Medline (including In-Process & Other Non-Indexed Citations), all Evidence Based Medicine reviews (EBM) (including Cochrane Database) and Scopus. Each database was searched with the following search terminologies (adapted to each database requirements): "airway OR upper OR nasal OR pharynx" and "segmentation OR reconstruction OR algorithm OR three dimensional imaging" and "cone beam computed tomography OR computed tomography". An example of search terminology used in Medline is summarized in table 2.1.1. (Search terminology for all EBM reviews and Scopus are provided in Appendix A)

Table 2.1.1: Example of search terminology in Medline

Keywords	**Number of articles**
1. Airway.mp.	94883
2. exp Pharynx/ or upper.mp.	39104
3. Nasal.mp. or exp Nasal Cavity/	80344
4. 1 or 2 or 3	194220
5. exp Algorithms/ or segmentation.mp.	159925
6. exp Tomography, X-Ray Computed/ or cone beam computed tomography.mp. or exp Cone-Beam Computed Tomography/	243627
7. 4 and 5 and 6	**138**

Two reviewers conducted the selection process independently. In case of disagreement, discussion between both reviewers was favoured to reach a consensus.

Phase I: the first phase of the selection process involved reviewing the titles and abstracts of the potential articles according to the following inclusion criteria:

- Upper airway assessment, and
- Use of CBCT.

Phase II: the second phase consisted of a detailed review of the entire retrieved article as selected in phase I. In addition to the initial selection criteria, two more were added at this stage:

- Only studies that involved an automated or semi-automated, three-dimensional/volumetric segmentation of the upper airway were selected.

- In studies involving a physical/geometric model, the design of the airway model must mimic the possible different diameters/shapes or angles of the human airway.

Finally, manual search of potentially missing articles was completed using the references/bibliography of the articles identified at phase II. In addition, the authors of the selected studies were contacted to inquire about missing or incomplete data.

A customized systematic evaluation protocol (table 2.1.2) was created to assess systematically the selected studies. For example, a study that included a randomized sample of human subjects, $\geq$ 30, preferably included a test group with abnormal airway, used manual segmentation as gold standard, analyzed the entire upper airway with several types of measurements, and executed proper statistical analyses would score higher and would be considered scientifically superior to that of another study that scores less. Accordingly, any conclusions withdrawn from any of these sixteen articles had to be based on studies that scored higher i.e. were superior in design and analysis. Because the accuracy of an airway model should be checked against a gold standard, ideally manual segmentation, and by means of reliable measurements, more points were given to the parts "Study measurements" and "Data analysis" in table 2.1.2 "Study design" was taken into consideration, however was given fewer points. No efforts were made to validate this evaluation tool. In addition, the parameters of CBCT scan protocol used in the final selected articles were also collected.

Table 2.1.2: Evaluation checklist for the final selected studies

Parameters of Evaluation			Maximum score
1. Study design	a.	Randomized sample (✓)	1
	b.	Sample size ≥ 30 (✓)	1
	c.	Test group included (✓)	1
	d.	Physical model (✓) Human (✓)	2
	e.	Method of segmentation Algorithm (✓) Commercial software (✓)	1
2. Study measurement	f.	Validation/Gold standard Physical model (✓ ✓ ✓) Manual segmentation (✓ ✓ ✓ ✓)	4
	g.	Part of airway Oropharynx/nasopharynx (✓) nasal cavity (✓) paranasal sinuses (✓)	3
	h.	Type of measurement Linear (✓) Area (✓) Shape (✓) Volume (✓ ✓)	5
3. Data Analysis	i.	Reliability: Intra-examiner (✓) Inter-examiner (✓) Kappa or ICC (✓) Other statistical test: Appropriate (✓) P value, R^2 reported (✓)	5
			Total (✓) = 23

2.1.3 Results

Database search

The search results and the number of articles at each phase from the various databases are provided in table 2.1.3. Comparing the final results of the different databases, Scopus finally obtained the most articles (68.75%) whereas all EBM reviews originally obtained fifteen potential studies, but none were deemed useful per our selection criteria. By the end of phase II, ten studies were excluded either due to duplication or selection criteria and only twelve met the selection criteria. Finally, manual searching of the references from articles identified at phase II obtained four additional studies. The final number of articles deemed useful therefore was sixteen.

Table 2.1.3: Number of articles per database

Database	Medline	EBM reviews	Scopus	Hand search	Total articles
Initial search	138	15	75	-	228
Phase I	4*	0	18	-	22
Phase II	1	0	18$^{\Psi}$	-	19
Final selection	1	0	11	4	16
Contribution of database to final selection (%)	6.25%	0%	68.75%	25%	
***3 articles excluded at next phase: duplicates** **$^{\Psi}$7 articles excluded at next phase: violated selection criteria**					

Article scores and evaluation

The application of the customized evaluation tool is presented in table 2.1.4. Results and conclusions of articles that scored ≥50% were given more weight since these studies present more accurate methodology compared to other studies. Only five articles[9, 12, 13-15] scored over 50%. The study by El and Palomo[9] presented the highest score, 69.57%.

Table 2.1.4: Scores of the final sixteen selected studies using checklist

Studies evaluated	Parameters of scoring (x.: maximum score)									Total score n (% out of 23)
	Study Design					*Study measurements*			*Data analysis*	
	a.=1	b.=1	c.=1	d.=2	e.=1	f.=4	g.=3	h.=5	i.=5	
El and Palomo[9] 2011	1	1	0	2	1	4	2	2	3	16(69.57%)
Shi et al[12] 2006	1	0	0	2	1	4	1	4	0	13(56.52%)
Lenza et al[13] 2010	0	1	0	2	1	0	1	4	4	13(56.52%)
Haskell et al[14] 2009	0	0	0	2	1	0	1	5	4	13(56.52%)
Iwasaki et al[15] 2009	0	1	0	2	1	0	2	5	2	13(56.52%)
Grauer et al[16] 2009	0	1	0	2	1	0	1	3	3	11(47.82%)
Kim et al[17] 2010	0	0	0	2	1	0	2	4	2	11(47.82%)
Tso et al[18] 2009	1	0	0	2	1	0	1	4	2	11(47.82%)
Iannetti et al[19] 2011	0	0	1	2	1	0	1	3	3	11(47.82%)
Schendel and Hatcher[20] 2010	0	0	1	2	1	3	1	1	0	9(39.13%)
El et al[21] 2011	0	0	1	2	1	0	1	4	0	9(39.13%)
Iwasaki et al[22] 2011*	0	1	1	2	1	0	3	0	0	8(34.78%)
Schendel et al[23] 2011	0	0	0	2	1	0	1	3	0	7(30.43%)
Cheng et al[10] 2007	0	0	0	2	1	0	1	3	0	7(30.43%)
Huynh et al[7] 2009*	0	0	0	2	1	0	1	0	0	4(17.39%)
Celenk et al[24] 2009	0	0	0	2	1	0	1	0	0	4(17.39%)
***CFD (computational fluid dynamics) studies**										

Detailed analysis of the sixteen articles is summarized in table 2.1.5. Although there were few articles published in 2006 and 2007, the majority of the articles were recent (from 2009 to 2011). Most studies were not randomized, included subjects with normal/healthy airway, and utilized software products for the segmentation process. Only two studies[9, 12] used manual segmentation as a gold standard to validate their measurements and only eight[9,13-17,19,20] reported the reliability of their measurements. The majority of the articles included analysis of oro-naso-pharyngeal airway and one or more measurements (linear, area, or volume). In terms of data analysis, most studies did not score high for reliability or appropriate statistical tests. Two studies[7,22] were computational fluid dynamic studies (CFD) and did not include such measurements or statistical analysis.

Table2.1.5: Analysis of study methodology for the selected sixteen articles

	Study design **-Sample** **-Subjects** **-Software/algorithm**	Study measurements **-Gold standard** **-Airway region** **-Measurements**	Data analysis **-Reliability (IER)** **-Other statistical test**
El and Palomo[9] 2011	-randomized, n= 30 - normal airway - Dolphin3D®, InVivoDental®, OnDemand3D®	-Manual segmentation: OrthoSegment -ONpharynx & part of nasal cavity -Volume	- ICC - not appropriate
Shi et al[12] 2006	-randomized, n=20 - NR -Algorithm: Visual C++, VTK program language	-Manual segmentation; for 1 case only -ONpharynx -linear, area, and volume	-NR -not appropriate
Lenza et al[13] 2010	- Not randomized, n=34 - normal airway - Mimics®	-None -ONpharynx -Linear, area, and volume	-Dahlberg's formula and ANOVA -appropriate
Haskell et al[14] 2009	- not randomized, n= 26 - OSA - Dolphin3D®, Image J®	-None -ONpharynx-naso-pharynx -linear, area, shape and volume	- ICC -appropriate
Iwasaki et al[15] 2009	-Not randomized, n=45 -normal airway - INTAGE Volume Editor®	-None -ONpharynx -Linear, area, shape and volume	-paired t-test, correlation r, Dahlberg's formula -not appropriate
Grauer et al[16] 2009	-Not randomized, n=62 - normal airway - InsightSNAP®	-None* -ONpharynx -shape and volume	- COV -appropriate
Kim et al[17] 2010	-Not randomized, n=27 - normal airway - InVivoDental®	-None -ONpharynx- and nasal cavity -Linear, shape, and volume	- ICC -appropriate
Tso et al[18] 2009	- randomized, n=10 - normal airway - CBWorks®	-None -ONpharynx -Linear, area, and volume	-NR -appropriate
Iannetti et al[19] 2011	-Not randomized, n=4 -craniofacial syndromic malformations -Dolphin3D®	-None -Nasal cavity -area and volume	-Wilcoxon signed rank test -not appropriate
Schendel and Hatcher[20] 2010	-Not randomized, n=1 -OSA -Airway phantom -3dmDVultus®	-Phantom -ONpharynx -Measurements: **Phantom;** linear, area, and volume **OSA subject**; area only	-Mentioned (Phantom), NR (OSA subject) -Appropriate (Phantom), NR (OSA subject)

Table2.1.5: Continued

	Study design **-Sample** **-Subjects** **-Software/algorithm**	Study measurements **-Gold standard** **-Airway region** **-Measurements**	Data analysis **-Reliability (IER)** **-Other statistical test**
El et al[21] 2011	-Not randomized, n=1 -OSA -Dolphin3D® and OnDemand3D®	-None -ONpharynx -Linear, area, and volume	-NR -NR
Iwasaki et al[22] 2011*	-Not randomized, n= 40 -normal airway -INTAGE Volume Editor®/ refined by algorithm	-None -ONpharynx nasal cavity and paranasal sinuses -None/ CFD* study	-NR -NR
Schendel et al[23] 2011	-Not randomized, n=1 -OSA -3dmdVultus®	-None -ONpharynx -area and volume	-NR -NR
Cheng et al[10] 2007	-Not randomized, n=1 -NR -Algorithm: Modified GVF snakes	-None -ONpharynx -area and volume	-NR -NR
Huynh et al[7] 2009*	-Not randomized, n=4 -OSA -V-Works®, ImageJ®, Pro/engineer®	-None -ONpharynx -None/ CFD* study	-NR -NR
Celenk et al[24] 2009	-Not randomized, n=1 -NR -Algorithm: 3D Gaussian smoothing kernel, 3D PCA C^{++} programming	-None -ONpharynx -None	-NR -NR

ONpharynx: oro-naso-pharynx
IER: inter/intra-examiner reliability
ICC: Intra correlation coefficient
NR: not reported
OSA: obstructive sleep apnea
*CFD: computational fluid dynamics

®For details on software products reported in this systematics review, please refer to the original articles.

CBCT scan protocol

CBCT scan parameters/protocol used for each study is presented in table 2.1.6. The most common CBCT machines used were iCAT (Imaging Sciences International, Hatfield, PA, USA) and CB MercuRay (Hitachi Medical, Tokyo, Japan), five articles each. NewTom (3G, QR s.r.l.; AFP Imaging, Elmsford, NY, USA) and Master 3D dental-imaging system (Vatech, Seoul, Korea) were also used in one article each. The remainder four articles failed to mention the CBCT machine used in their protocol. In studies that reported their scanning protocol, the field of view (FOV) ranged from 13 cm to 30.5 cm, the mA from 2 to 15 and 110 or 120 kVp. The scanning time varied from 10 to 40 seconds and the resolution varied from 0.25-0.6mm voxel size/3.527x3.527 or 1024x1024 pixels.

Table 2.1.6: CBCT scan protocol collected from the selected sixteen articles

	CBCT machine	FOV	mA	Kvp	Time (seconds)	Resolution Voxel/pixel
El and Palomo[9] 2011	Hitachi CB Mercuray	12”	2	120	NR	1024x1024 pixel
Shi et al[12] 2006	iCAT	22 cm	NR	NR	20+20s	0.4mm voxel
Lenza et al[13] 2010	iCAT	NR	3-6	120	20s	0.4mm voxel
Haskell et al[14] 2009	NewTom	12”	1-4	110	36s /5.4s exposure	0.36mm voxel
Iwasaki et al[15] 2009	Hitachi CB Mercuray	NR	15	120	9.6s	0.377mm voxel
Grauer et al[16] 2009	iCAT	Medium or full	NR	NR	NR	0.3mm voxel
Kim et al[17] 2010	Master 3D dental imaging system	12”	NR	NR	NR	NR
Tso et al[18] 2009	Hitachi CB Mercuray	19 cm	10	120	10 s	0.6 mm voxel
Iannetti et al[19] 2011	NR	NR	NR	NR	NR	NR
Schendel and Hatcher[20] 2010	iCAT	13 cm	NR	NR	40s	0.25mm voxel
El et al[21] 2011	Hitachi CB Mercuray	NR	15	120	9.6 s	0.377 mm voxel
Iwasaki et al[22] 2011*	Hitachi CB Mercuray	12”	15	120	NR	1024x1024 pixel
Schendel et al[23] 2011	NR	NR	NR	NR	NR	NR
Cheng et al[10] 2007	NR	NR	NR	NR	NR	3.527x3.527 pixel
Huynh et al[7] 2009*	iCAT	23x19 cm	NR	NR	NR	0.4mm voxel
Celenk et al[24] 2009	NR	NR	NR	NR	NR	NR

FOV: field of view
mA: milliAmpere
kVp: kiloVoltage peak
NR: not reported

2.1.4 Discussion

CBCT technology has introduced a paradigm shift in oral and maxillofacial imaging by transitioning from 2D to 3D. 3D segmentation of the upper airway using CBCT paved the road to study the anatomy and function of narrowed airways in subjects with sleep disordered breathing, e.g. obstructive sleep apnea (OSA), in ways that were unattainable before.[25] Most 3D airway models generated from CBCT have not been validated in the literature.[9]

Study design

Only few studies[9,12,18] were randomized and a sample size more than 30 was found in only five studies[9,13,15,16,22]. Accordingly, these studies should have less bias in their measurements. In three articles[10,13,24], the authors attempted the use of reconstruction algorithms instead of commercial software. Because the main purpose of these studies was to develop new or modify previous reconstruction methods using different algorithms, the sample size was smaller than that for studies using commercial software, and study measurements were limited if not absent. Most articles analysed subjects with healthy upper airways. Five articles[7,12,20,22,23] analysed constricted airways of subjects with OSA. Studies by Lenza et al[13], Cheng et al[10], and Celenk et al[24] failed to report whether the analysed airway was that of a healthy subject or OSA patient. No study, out of the sixteen, compared the accuracy of 3D airway model between OSA patients and their healthy controls. If an OSA subject is an obligatory mouth breather or if the CBCT scan time was long, the patient would undergo multiple breathing cycles thus causing some motion artefact that can affect the resolution of the airway boundaries. This technical difficulty was not addressed by any of the studies that included OSA subjects.

Study measurements

Validity is defined in this systematic review as agreement in measurements between the software or segmentation algorithm and the gold standard/or ground truth. Reliability or reproducibility is defined as the agreement between measurements within the same examiner (intra-examiner) or between different examiners (inter-examiner) using a commercial software or reconstruction algorithm.

Out of the sixteen articles, only three[9,12,20] tested their measurements against a gold standard. Out of these, El and Palomo[9] and Shi et al[12] used manual segmentation as a reference. El and Palomo[9] validated their measurements for the entire sample of 30, whereas Shi et al[12] validated their measurements with manual segmentation in only one case. Grauer et al[16] stated that the segmentation process/software they used was described and validated previously by Yushkevich et al[26] and was superior to manual segmentation. However, Yushkevich et al[26] validated InsightSNAP® (version 1.4.0, Cognitica, Philadelphia, PA, USA) using magnetic resonance images (MRI) not CBCT. Clearly, MRI and CBCT are very different imaging modalities with different image resolution that can affect the accuracy of segmentation significantly. 3D airway models generated from CBCT are being introduced as an objective evaluation tool of surgical treatment of OSA subjects, orthognathic surgeries, and maxillary expansion and their impaction on airway dimensions. This necessitates a proper, scientific validation of the method used to generate this model as it serves as baseline for treatment.

Schendel and Hatcher[20] used measurements of an airway phantom as validation; however the true complex anatomy of the human airway cannot be replicated and measured physically, hence the use of the airway phantom with uniform geometry. Therefore, manual segmentation,

which by default should better represent ground truth, would be the ideal gold standard for segmentation especially in the nasopharynx and nasal cavity.

Most authors analysed the pharyngeal airway with volumetric measurements. Only Iannetti et al[19], Iwasaki et al[22] and El and Palomo[9] segmented the nasal cavity and/or maxillary sinuses. The shape of the oropharyngeal airway is similar to a tube and is completely hollow. This makes the process of segmentation straightforward. The anatomy of the nasal cavity is complicated with the narrow and tortuous pathways of the conchae and meatuses, consequently the segmentation process is extremely challenging due to difficulties encountered in defining the boundaries and grey-thresholding especially with noisy CBCT images. Therefore, studies that only focus into the oropharyngeal airway will likely over-represent the true validity of the evaluated tools.

Three studies[7,22,24] failed to report any linear, area or volumetric measurements. Studies by Iwasaki et al[22] and Huynh et al[7] were computational fluid dynamic (CFD) studies where the measurement of airflow, velocity, pressure and resistance were the parameters of concern. CFD studies simulate airflow in the airway to assess the functional changes in the airway rather than anatomical and/or visual analysis of the airway. The main focus of Celenk et al[24] was to develop a user friendly method to detect and construct 3D human airway using CBCT and while the use of 3D Gaussian smoothing kernel seemed very promising, the authors could've attempted to validate their proposed method by comparing area and volumetric measurements of the airway against manual segmentation.

Data analysis

The quality of statistical analysis used in the majority of the articles was poor. To measure the validity, ICC (intra-class correlation coefficient) is the most appropriate statistical tool. ICC is a general measurement of agreement or consensus. It is an improvement over Pearson's r and Spearman's ρ, as it takes into account the differences in ratings, along with the correlation between raters.[27,28]

El and Palomo[9] validated their human airway model by means of volumetric measurement against manual segmentation however did not use ICC. Instead, they used linear regression analysis and reported paired t-test and Pearson correlation coefficient, *r*, to validate their measurements. Shi et al[12] validated their human airway model by means of linear measurement against manual measurement however did not use ICC. The authors used paired t-test to report the differences in linear measurement. Linear regression analysis provides information about the linear relationship or correlation between two random variables, not agreement.[29]

To measure *reliability or reproducibility*, ICC is the most appropriate test tool. Only three studies[9, 14, 17] used ICC for their intra-examiner agreement (IEA) however, none reported the ICC's 95% confidence interval (CI). The lower limit of the ICC's CI reports how small the examiner agreement might be. For example, if the ICC yielded ≤ 0.80 and the lower bound of CI was 0.60 this does not necessarily imply good agreement. Lenza et al[13] and Iwasaki et al[15] used Dahlberg's formula to detect errors between measurements. Springate[30] examined the use of Dahlberg's formula to estimate errors and found that Dahlberg's formula can under or overestimate the true value of the random error.

Grauer et al[16] used coefficient of variation (COV) and Iannetti et al[19] used Wilcoxon sign rank test to measure reliability of volumetric measurements. COV is a measure of dispersion and Wilcoxon sign test detects differences in the means, however none of these tests measures "agreement".

In terms of statistical tests used to analyse the possible relationship and/or correlation between the different airway dimensions and craniofacial parameters, most authors mistakenly used univarite statistical tests, e.g. *t*-test, for each variable instead of using multivariate analysis for all the variables tested. In doing so, the alpha (error type I) is inflated and possible inter-correlation between the variables was ignored. Haskell et al[14] used multiple linear regression to analyse 7 predictors and over 12 outcome variables and had a sample size of 26 only. This can affect the power of the regression model.

To summarize, El and Palomo[9] were the only authors to test the accuracy of airway models against manual segmentation. In their study, they reconstructed the pharyngeal airway and part of the nasal cavity, separately, and used volumetric measurements in 30 CBCT image sets. They concluded that the volumetric measurements of the three software products tested: Dolphin3D **(**version 11, Dolphin imaging & Management Solutions, Chatsworth, CA, USA), InVivo- Dental (version 4.0.70, Anatomage, San Jose, CA, USA), and OnDemand3D (version 1.0.1.8407, CyberMed, Seoul, Korea) were reproducible and had high correlation with the measurements of manual segmentation however were not valid. In other words, the software consistently over or underestimated the true, manual, volumetric measurements hence the high correlation and therefore were not accurate, suggesting "systematic errors". However, the reader has to keep in mind that the authors measured "linear" correlation, by using linear regression, instead of ICC to measure the validity. The largest difference was found between

OnDemand3D® and manual segmentation in the oropharyngeal airway volume, -2163.25mm^3 (95% CI= -2945.69 mm^3, -1380.80 mm^3). Although this difference was found statistically significant, it is uncertain if it would be of clinical significance. It is unclear whether linear and volumetric measurements are sufficient parameters that can be used to validate 3D airway models and are accurate indicators/predictors of surgical outcomes. Perhaps it would be more meaningful if airway models were analysed not only based on measurements but also on geometrical assessment using shape analysis.

CBCT protocol

When reported, most of the studies used CBCT machines that required the patient to be seated. Lenza et al[13] used the NewTom®, which requires the patient to be supine. It has been shown that the dimension of the airway changes from sitting to supine position mostly due to the relaxation of the soft palate, tongue and change in hyoid bone position.[31] Since patients are awake during the CBCT scan and sleeping conditions are not simulated, the airway should be, in our opinion, imaged while patients are seated.

Studies that reported CBCT's field of view (FOV) used FOV ranging from 13 to 30.5 cm. 13 cm FOV is acceptable to image one part of the upper airway (oropharynx or nasal cavity) larger dimensions are satisfactory to image the entire upper airway (superior limits of nasal cavity to epiglottis inferiorly). A kilo Voltage peak (kVp) of 120 was used in most studies and milliAmperage (mA) ranged from 1 to 15. Whether the kVp or mA was fixed or adjustable, it depends on the CBCT machine used. If these parameters were adjustable, none of the authors explained why they selected these specific scanning parameters. The scan time highly varied (9.6 to 40 seconds) and the voxel size ranged from 0.25 to 0.6 mm. This is also dependant on the CBCT machine as well as the operator's selection and was not explained or justified by any of

the authors. Conceptually, increasing the kVp, mA, scan time and reducing the voxel size will gain the highest resolution for optimum segmentation of the airway, however, at the expense of radiation dose to the patient.[32] This was not addressed in any of the articles included.

In conclusion, only three articles (out of 16) properly tested the reliability of 3D upper airway models generated from CBCT and only one article had a sound methodology to test their accuracy. The literature lacks scientific justification of a solid and optimized CBCT protocol for airway imaging. Due to the limited number of adequate studies, it is difficult to generate a strong conclusion regarding the validity and reliability of CBCT-generated 3D models.

2.1.5 References

1. 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. *Journal of Oral and Maxillofacial Surgery.* 2011;69:677-686.

2. 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;15:63-69.

3. Aboudara CA, Hatcher D, Nielsen IL, Miller A. A three-dimensional evaluation of the upper airway in adolescents. *Orthodontics & craniofacial research.* 2003;6 Suppl 1:173-175.

4. Miles PG, Vig PS, Weyant RJ, Forrest TD, Rockette HE Jr. Craniofacial structure and obstructive sleep apnea syndrome-a qualitative analysis and meta-analysis of the literature. 1996; 109: 163-72. *Am J Orthod Dentofacial Orthop.* 1996;109:163-72.

5. Yu X, Fujimoto K, Urushibata K, Matsuzawa Y, Kubo K. Cephalometric analysis in obese and nonobese patients with obstructive sleep apnea syndrome. *Chest.* 2003;124:212-8.

6. 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. *American Journal of Orthodontics and Dentofacial Orthopedics.* 2009;135:468-479.

7. Huynh J, Kim D, McQuilling M. Pharyngeal airflow analysis in obstructive sleep apnea patients pre- and post-maxillomandibular advancement surgery. *J of fluids Eng.* 2009;131:091101-091111.

8. Osorio F, Perilla M, Doyle DJ, Palomo JM. Cone beam computed tomography: An innovative tool for airway assessment. *Anesth Analg.* 2008;106:1803-1807.

9. El H, Palomo JM. Measuring the airway in 3 dimensions: A reliability and accuracy study. *American Journal of Orthodontics and Dentofacial Orthopedics.* 2010;137:S50.e1-S50.e9.

10. Cheng I, Nilufar S, Flores-Mir C, Basu A. Airway segmentation and measurement in CT images. *Conference proceedings : ...Annual International Conference of the IEEE Engineering in Medicine and Biology Society.IEEE Engineering in Medicine and Biology Society.Conference.* 2007;2007:795-799.

11. Ogawa T, Enciso R, Shintaku WH, Clark GT. Evaluation of cross-section airway configuration of obstructive sleep apnea. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2007;103:102-108.

12. Shi H, Scarfe W, Farman A. Upper airway segmentation and dimensions estimation from cone-beam CT image datasets. *Int J CARS.* 2006;1:177-186.

13. Lenza MG, de O. Lenza MM, Dalstra M, Melsen B, Cattaneo PM. An analysis of different approaches to the assessment of upper airway morphology: A CBCT study. *Orthodontics and Craniofacial Research.* 2010;13:96-105.

14. Haskell JA, McCrillis J, Haskell BS, Scheetz JP, Scarfe WC, Farman AG. Effects of mandibular advancement device (MAD) on airway dimensions assessed with cone-beam computed tomography. *Semin Orthod.* 2009;15:132-158. doi:DOI: 10.1053/j.sodo.2009.02.001.

15. Iwasaki T, Hayasaki H, Takemoto Y, Kanomi R, Yamasaki Y. Oropharyngeal airway in children with class III malocclusion evaluated by cone-beam computed tomography. *American Journal of Orthodontics and Dentofacial Orthopedics.* 2009;136:318.e1-318.e9.

16. Grauer D, Cevidanes LSH, Styner MA, Ackerman JL, Proffit WR. Pharyngeal airway volume and shape from cone-beam computed tomography: Relationship to facial morphology. *American Journal of Orthodontics and Dentofacial Orthopedics.* 2009;136:805-814.

17. Kim Y-, Hong J-, Hwang Y-, Park Y-. Three-dimensional analysis of pharyngeal airway in preadolescent children with different anteroposterior skeletal patterns. *American Journal of Orthodontics and Dentofacial Orthopedics.* 2010;137:306.e1-306.e11.

18. Tso HH, Lee JS, Huang JC, Maki K, Hatcher D, Miller AJ. Evaluation of the human airway using cone-beam computerized tomography. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontology.* 2009;108:768-776.

19. Iannetti G, Polimeni A, Pagnoni M, et al. Upper airway volume after le fort III advancement in subjects with craniofacial malformation. *J Craniofac Surg.* 2011;22:351-5.

20. Schendel SA, Hatcher D. Automated 3-dimensional airway analysis from cone-beam computed tomography data. *Journal of Oral and Maxillofacial Surgery.* 2010;68:696-701.

21. El AS, El H, Palomo JM, Baur DA. A 3-dimensional airway analysis of an obstructive sleep apnea surgical correction with cone beam computed tomography. *Journal of Oral and Maxillofacial Surgery.*;In Press, Corrected Proof doi:DOI: 10.1016/j.joms.2010.11.046.

22. Iwasaki T, Saitoh I, Takemoto Y, et al. Evaluation of upper airway obstruction in class II children with fluid-mechanical simulation. *American Journal of Orthodontics and Dentofacial Orthopedics.* 2011;139:e135-e145.

23. Schendel S, Powell N, Jacobson R. Maxillary, mandibular, and chin advancement: Treatment planning based on airway anatomy in obstructive sleep apnea. *Journal of Oral and Maxillofacial Surgery.* 2011;69:663-676.

24. Celenk M, Farrell ML, Eren H, Kumar K, Singh GD, Lozanoff S. Upper airway detection and visualization from cone beam image slices. *Journal of X-Ray Science and Technology.* 2010;18:121-135.

25. Hatcher DC. Cone beam computed tomography: Craniofacial and airway analysis. *Sleep Medicine Clinics.* 2010;5:59-70.

26. Yushkevich PA, Piven J, Hazlett HC, et al. User-guided 3D active contour segmentation of anatomical structures: Significantly improved efficiency and reliability. *Neuroimage.* 2006;31:1116-1128. doi:DOI: 10.1016/j.neuroimage.2006.01.015.

27. Koch, Gary G. "Intraclass correlation coefficient". Encyclopedia of Statistical Sciences. 1982; 4th Ed. Samuel Kotz and Norman L. Johnson. New York: John Wiley & Sons. 213–217.

28. Reinhold Müller & Petra Büttner. A critical discussion of intraclass correlation coefficients. Statistics in Medicine.1994; 13(23-24): 2465–2476.

29.Zou KH, Tuncali K, Silverman SG. Correlation and simple linear regression. *Radiology.* 2003;227:617-622. doi:10.1148/.

30. Springate SD. The effect of sample size and bias on the reliability of estimates of error: A comparative study of dahlberg's formula. *The European Journal of Orthodontics.* 2011 doi:10.1093/ejo/cjr010.

31. Battagel JM, Johal A, Smith A-, Kotecha B. Postural variation in oropharyngeal dimensions in subjects with sleep disordered breathing: A cephalometric study. *Eur J Orthod.* 2002;24:263-276.

32. Palomo JM, Rao PS, Hans MG. Influence of CBCT exposure conditions on radiation dose. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology.* 2008;105:773-782. doi:DOI: 10.1016/j.tripleo.2007.12.019.

2.2 CBCT assessment of upper airway changes and treatment outcomes of obstructive sleep apnea: a systematic review*

N. Alsufyani, M. Al-Saleh, P. Major

*Published in *Sleep and Breathing* 2013;17(3):911-23

2.2 CBCT assessment of upper airway changes and treatment outcomes of obstructive sleep apnea: a systematic review

Abstract

Objective: To review studies using cone beam computed tomography (CBCT) to assess dimensional changes in the upper airway after appliance or surgical therapy in subjects with obstructive sleep apnea and to correlate CBCT findings with treatment outcome. **Method:** Several electronic databases were searched. Studies that met selection criteria were evaluated using a customized evaluation tool. **Results:** Study parameters were met in seven articles. Fifty adults were assessed using CBCT 1.6-10 months after appliance therapy or maxillary-mandibular advancement (MMA) surgery with Genial Tubercle Advancement (GTA). Airway parameters measured were linear, cross-sectional (CS) area, volume, or airway function. In only two validated surgical case reports, airway volume increased by 6.5-9.7 cm^3 (> 80%) and minimum CS area by 0.1-1.2 cm^2 (21% and 269%). **Conclusion**: The available published studies show evidence of CBCT measured anatomic airway changes with surgery and dental appliance treatment for OSA. There is insufficient literature pertaining to the use of CBCT to assess treatment outcomes to reach a conclusion. High quality-evidence level studies, with statistically appropriate sample sizes, and cross validated clinically are needed to determine if CBCT airway dimensional changes are suitable for assessment of treatment outcome.

2.2.1 Introduction

Sleep-disordered breathing (SDB) is a spectrum of conditions with abnormal respiratory pattern and/or decreases in oxyhemoglobin saturation during sleep.[1, 2] Obstructive sleep apnea syndrome (OSA) is the severe end of that spectrum[1, 3]. Recently, OSA is being seen in greater numbers even within the paediatric and adolescent age range.[4] OSA may affect 2%-4% of middle-aged adult population in North America and 2- 3% children.[1, 3, 5-7]In the 2009 Wisconsin Sleep Cohort Study, the reported SDB prevalence was 9% in women and 24% in men, based on Apnea Hypopnea index (AHI) > 5 [8].

Management of OSA may include one or more of: conservative approach (e.g. diet or altering sleep position), Continuous Positive Airway Pressure *CPAP*, oral appliance therapy (e.g. Mandibular Advancement Devices), and surgery.[4, 9] Currently, oral appliances are underused partly due to their cost and difficulties faced by dentists to utilize these appliances or control their various dental side effects.[10]

Obstruction can occur at single or multiple levels along the upper airway, from the tip of the nose to the larynx.[11] Imaging of the upper airway has traditionally employed lateral cephalometric radiography. Cephalometry is informative and readily available however possess the limitations of any two-dimensional (2D) radiographic procedure: changes which occur in the transverse dimension cannot be visualized.[12] 3D imaging modalities, including cone beam CT, multi-detector CT, and magnetic resonance imaging (MRI), allow 3D segmentation and analysis of organs of interest. This provides an opportunity to evaluate functional and developmental relationships between skeletal, oral, and pharyngeal dimensions between OSA subjects and their normal peers as many SDB subjects presented with narrow upper airway.[13-15] Advanced imaging modalities demonstrated diminished airway prior to treatment and the significant changes that

occur following successful treatment however, conflicting results have been reported.[4, 16] The ability to identify the location or cause of obstruction in an attempt to clarify treatment efficacy will continue to improve.[13, 17] Ultimately, the diagnostic study should provide anatomic and functional imaging consistent with the physiologic location and severity of disease with minimal invasion, limited radiation exposure, and relevance to treatment.[11] CBCT devices have become available for oral and maxillofacial imaging, including the upper airway, at a reduced radiation and cost.[12, 18, 19] Accordingly, several disciplines in dentistry are capable of providing or assessing treatment for patients with or at risk for OSA.[4, 20, 21]

The use of CBCT to investigate upper airway obstruction in patients with SDB/OSA and its usefulness to assess treatment outcome has not been systematically reviewed. The purpose of this review is to answer the following questions:

1) For appliance or surgical therapy, can CBCT measured dimensional airway changes serve as an objective tool to assess treatment outcomes (measured by AHI) in subjects with SDB/OSA? And if so,
2) Which upper airway sites are most sensitive to depict treatment success? What is the magnitude of the change in these sites?

2.2.2 Methods

Database search

A systematic search of multiple electronic databases was completed during the last week of April 2012. Databases searched were: Medline (including In-Process & Other Non-Indexed Citations), all Evidence Based Medicine reviews (EBM) (including Cochrane Database) and

Scopus. Each database was searched with the following search terminologies (adapted to each database requirements): “Obstructive sleep apnea OR Sleep Apnea Syndromes OR sleep disordered breathing” and “Cone-Beam Computed Tomography OR Computed tomography OR Tomography, X-Ray Computed”. The search terminology used in Medline is summarized in table 2.2.1. Search terminology for all electronic databases is provided in Appendix A.

Table 2.2.1: Medline electronic database search

	Keywords	**#hits**
1	Obstructive sleep apnea.mp. or exp Sleep Apnea, Obstructive/	13,324
2	Sleep disordered breathing.mp. or exp Sleep Apnea Syndromes/	20796
3	1or2	22291
4	cone beam CT.mp. or exp Cone-Beam Computed Tomography	2,211
5	exp Tomography, X-Ray Computed/ or computed tomography.mp.	310244
6	4 or 5	310351
7	3 and 6	355

Two reviewers (NA and MA) conducted the selection process independently. In case of disagreement, discussion between both reviewers was favoured to reach a consensus.

Inclusion criteria:

- Use of CBCT.
- Subjects diagnosed with sleep disordered breathing or obstructive sleep apnea syndrome.
- Only studies that involved intervention to treat SBD/OSA were selected.

Exclusion criteria:

- Editorials, commentaries, or reviews.
- Cadaver studies.
- Multi-detector or spiral CT.

The screening process consisted of three phases:

Phase I: Review the titles and abstracts.

Phase II: Full article reading based on articles selected from Phase I.

Phase III: Hand/manual search of bibliography/references of articles from Phase II.

Quality and risk of bias assessment

A customized tool was created and adopted from the recommendations by Viswanathan et al [22] for assessing the risk of bias of individual studies in systematic reviews. The items of evaluation are based on study design and subject recruitment (selection bias), methods to assess the intervention and outcome (detection/measurement bias), statistical tests and their interpretation (analysis/interpretation bias), and effects of concurrent intervention (performance bias).

This tool was developed and tested using studies that fulfilled most of the selection criteria however were excluded due to the use of multi-detector CT. Using five of these studies, two viewers were trained to use this evaluation tool followed by a pilot test using different five studies. Issues and conflicts were identified from the training and pilot testing and the tool was revised to reach consensus. Finally, both reviewers independently assessed the final articles included in this systematic review using the finalized customized evaluation tool, table 2.2.2. The inter-examiner agreement was calculated using intra-class correlation coefficient (ICC).

Table 2.2.2: Risk of bias evaluation tool[§]

A. Selection bias	1.	Randomized sample		
	2.	Sample size ≥ 30		
	3.	Adequate test group • Were cases selected appropriately (e.g., appropriate diagnostic criteria or definitions)		
	4.	Adequate control group • Inadequate: does not match the test group		NA
	5.	Inclusion/exclusion criteria for recruitment		NA
B. Detection or measurement bias	6.	Adequate follow-up • Inadequate: loss to follow-up was a concern or follow-up period was not the same between groups.		
	7.	Was the intervention assessed using a reliable measure? i.e. sleep apnea assessment • Example: with PSG (gold standard), Pulse oximetry, QOL or sleep questionnaires, or others.		
	8.	Were the outcomes assessed using a reliable measure? i.e. CBCT measurements • Example: Inter or intra-examiner agreement reported		
	9.	Outcome assessors blinded to intervention.		
	10.	Reported and statistically controlled for confounding factors.		
C. Analysis or interpretation bias	11.	Adequate statistical tests used. • Inadequate: e.g. univariate analysis for multivariate outcomes		NA
	12.	Adequate and complete reporting of results • Inadequate: e.g. lack of SD or 95% CI, reporting significance based on *P* value when R^2/correlation is <50%.		NA
D. Performance bias	13.	Did researchers rule out any impact from a concurrent intervention or an unintended exposure that might bias results?		NA
			Total maximum score= 13	

§(adopted from recommendations by Viswanathan et al[21])
*NA: not applicable items:
For items 4 and 5: not applicable in single case reports
For items 11 and 12: not applicable in descriptive results.
For item 13: not applicable in the absence of concurrent treatment
For remainder items: if not reported, score NO.

Data analysis

For each study, demographic and clinical information were collected. In addition, SDB/OSA measurements, upper airway parameters (qualitative and/or quantitative) from CBCT analysis, and CBCT protocol were collected for each study.

2.2.3 Results

Database search

The search results and the number of articles are provided in the flow diagram in Figure 2.2.1. The electronic database search resulted in 705 articles. By the end of phase I, a total of 688 studies were excluded either due to duplication or selection criteria and only 17 were eligible to move into phase II. By the end of phase II, 10 out of the 17 studies were excluded and only 7 met the selection criteria. Finally, manual search of the references from articles identified at phase II did not obtain any additional studies. The final number of articles deemed useful therefore was seven, included adult OSA population, and were published between the years 2009 to 2011.

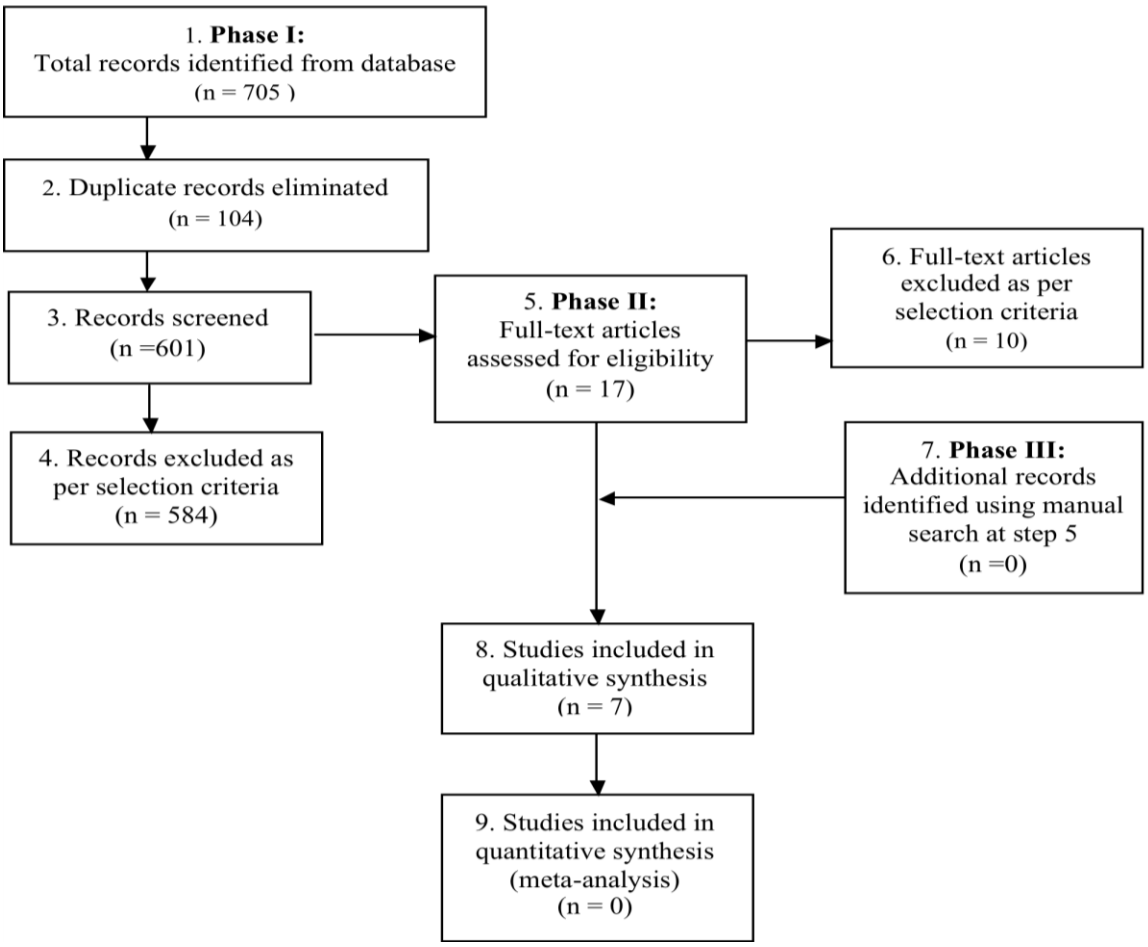


Figure2.2.1: Flow diagram with search strategy and number of articles.

Quality and research bias

Using the customized evaluation tool, the ICC between the two reviewers was 97.7% [95% confidence interval= 88.1-99.6%] indicating excellent intra-examiner agreement beyond chance. A study scoring 0- <50%, is graded as high risk of bias. Studies scoring 50% are graded as moderate risk of bias and those scoring >50% are of low risk of bias. The final score (%) of each article is provided in tables 2.2.3 and 2.2.4. All articles were either case reports or case series and the overall risk of bias was high (< 45%); mostly related to selection and detection or measurement bias.

Table 2.2.3: Data analysis for studies with appliance therapy

Variables collected			Study/year					
			AbiRamia et al[28]/2010		Haskell et al[26]/ 2009[†]		Singh et al[27]/ 2011	
Risk of bias Score= % Type of intervention Amount of advancement*			40.06% Modified Twin Block (TB) (75% of maximum protrusion)		32.04% MAD: Herbst appliance (4.0±3.6 mm^3)		20.0% Mandibular appliance & new maxillary DNA (maxilla inter-molar width: 5mm. mandible: 2.9mm)	
Demographic/ clinical data	-Sample size: gender -Age -BMI -Skeletal/dental factors -Follow-up period		- n= 16: 10 f, 6 m - Mean= 47.06 years - BMI <27 - Arch-overjet at least 4mm - Average 7 months		- n= 26: 9 f, 17 m - NR - NR - NR - NR		- n=1: m - 36 years -BMI: NR - Mid-facial underdevelopment - 10 months	
OSA parameters	Before	After	Mild/moderate OSA <u>PSG</u> - AHI<30	NR	Mild OSA <u>PSG</u> - AHI=+5	NR	Moderate OSA <u>PSG</u> -AHI=24/h -OxHm 90%	-Normal breathing <u>Home sleep test</u> -AHI= 0 -O_2 88-95% - Pulse63/min
	- severity - <u>Test</u>							

Table 2.2.3: continued

Variables collected		AbiRamia et al[28]/2010	Haskell et al[26]/ 2009[†]	Singh et al[27]/ 2011
CBCT airway parameters*	-Part of airway -Variable measured: With-without appliance= difference	- OP and partial NP -Total volume (mm^3): (8710±2813)-(7601±2659)= 1109±154	-OP - Change in total volume (m±SD)= 2792.8±4380.9 mm^3 - Change at MinCS MinCS/Lat= 2.5±4.7 mm MinCS/AP= 0.6±2.5mm MinCS/L:AP= 0.2±0.9 MinCS area= 43.2±86.2 mm^2 - Change at LgCS LgCS/Lat= 3.7±6.0 mm LgCS/AP= 0.8±2.1 mm LgCS/L:AP= 0.1±0.5 LgCS area= 71.4±61.7 mm^2 - Change at C2CS C2CS/Lat= 4.3±4.4 mm C2CS/AP= 1.0±2.1mm C2CS/L:AP= 0.2±0.5 C2CS area= 77.6±111.2 mm^2	- OP and partial NP - Total volume mm^3: 22024-12889 = (9135) -MinCS area: Visual/plot of increase.
Summary		-Total volume increase by 1.1±0.2 cm^3 (15±6%); statistically not significant *P*=0.0494 Change in airway outcome not validated against OSA measurement.	-Total volume increase by 2.8±4.4 cm^3 -Increase in MinCS area by 0.4±0.9cm^2 -Increase in AP dimension by 0.1cm. (largest at C2) -Increase in Lat dimension ranged from 0.3 to 0.4 cm. (largest at C2) -Overall, all airway parameters increased; statistically significant based on Z scores. Change in airway outcome not validated against OSA measurement.	-Total volume increase by 9.1cm^3 (71%) -Hx and concurrent use of CPAP. Change in airway outcome not validated against consistent OSA measurement.

*All measurements were rounded-up to one decimal.
† % of change in airway parameters was not feasible; original article provided mean change in airway dimensions only.
Abbreviations: *MAD*: mandibular advancement; *DNA*: Day-night appliance; *BMI*: body mass index; *NR*: not reported; *PSG*: polysomnography; *AHI*: Apnea-hypopnea index; *OxHm*: oxygenated haemoglobin; *OP*: oropharynx; *NP*: nasopharynx; *MinCs*: minimum cross section; *Lat*: lateral; *AP*: antero-posterior; *lgCs*: largest cross section; *C2Cs*: cross section at 2nd cervical vertebra; *Hx*: history; *CPAP*: Continuous positive airway pressure.

Table 2.2.4: Data analysis for studies with surgical intervention

Variables collected and summary		Study/year			
		El et al[25]/ 2011	Schendel et al[24]/ 2010	Schendel et al[29]/ 2011	Huynh et al[23]/ 2009 [CFD]
Study quality score %		33.33%	18.75%	33.33%	20.0%
Type of intervention (Amount of advancement)*		MMA + GTA (mandible:7mm, maxilla 6 mm)	MMA+GTA+GGA (10 mm)	-MMA + GTA (12mm)	MMA (mean: 4mm maxilla, 7.7mm mandible)
Sample size :gender		n=1: f	n= 1: f	n=1: m	n=4: 3m, 1 f
Age		32 years	55 years	54 years	mean 40 years
BMI		BMI =23.8	NR	NR	NR
Skeletal/dental		Mild skeletal Class II	Bimaxillary retrusion	Skeletal class III	NR
Follow-up period		6 months	NR	3 months	At least 7 weeks (1.6 months)
OSA parameters	Before | After	Severe OSA / Mild OSA	-Moderate OSA /	severe OSA / -Mild OSA	NR / NR
	Severity	PSG AHI=33.7 / PSG AHI=6.7	PSG AHI=19.9 / NR	PSG AHI=21 / PSG AHI=5	
	Test	Sleep Q -Epworth sleepiness scale 9/24 / Sleep Q -Epworth sleepiness scale 4/24		O_2 desat 82%	
CBCT airway parameters*	Part of airway	OP and partial NP	OP and partial NP*	OP and partial NP	OP and partial NP
	Variable measured: Pre-Post= difference	Total volume (mm^3): 7957.8 -14433.5= 6.5cm^3. MinCS area (mm^2): 46.3 - 170.7= (1.2 cm^2). Linear (mm): H-palate/AP: 16.2 -17.9=1.7(10.5%) H-palate/Lat: 12.6 -22.6=10 (79.4%) S-palate/AP: 1.8 -7.5=5.7 (316.7%) S-palate/Lat: 11.9 -23.2=11.3 (95.0%) Tongue/AP: 4.1 -9.2=5.1 (124.4%) Tongue/Lat: 13.9 - 21.5=7.6 (54.7%) C3/AP: 12.6 -13.5=0.9 (7.1%) C3/Lat: 17.8 -32.7=14.9 (83.7%)	MinCS area (mm^2): 6.6 - 112.4= (1.1 cm^2)	Total volume (mm^3) 10970 – 20690= 9720 MinCS area (mm^2): 59.5 – 72.0= 12.5	Total pressure drop (Pa) from T_0-T_1

Airflow	340 ml/s	400 ml/s	460 ml/s
Subj1	11.6	15.6	20.4
Subj2	21.3	28.8	37.4
Subj3	-0.3	-0.4	-0.6
Subj4	42.4	57.9	75.9

Airway resistance (%) from T_0-T_1

Airflow	340 ml/s	400 ml/s	460 ml/s
Subj1	-91.2	-91.3	-91.4
Subj2	-91.2	-91.3	-91.4
Subj3	+11.1	+12.5	+13.7
Subj4	- 97.5	- 97.6	- 97.7

Table 2.2.4: Continued

	El et al[25]/ 2011	Schendel et al[24]/ 2010	Schendel et al[29]/ 2011	Huynh et al[23]/ 2009 [CFD]
Summary	Total volume increase by 6.5cm^3 (81.0%) Increase in MinCS area by 1.24 cm^2 (269%) Increase in AP dimension ranged from 0.1 (7%) to 0.6 cm (317%). (largest at S-palate) Increase in Lat dimension ranged from 0.8 (55%) to 1.4 (95%) cm, largest at S-palate Clinically significant; however lacks statistical power Hx of CPAP; unknown duration.	Increase in MinCS area by 1.1 cm^2 (1598%) Change in airway outcome not validated against OSA measurement.	Total volume increase by 9.7 cm^3 (89%) Increase in MinCS area by 0.1 cm^2 (21%) Hx of conservative, mand positioning devices, uvular surgery; unknown duration	3 of 4 subjects showed reduction in total pressure along the airways and over 90% reduction in airway resistance. The remainder subject demonstrated opposite findings. Both outcomes increase in magnitude as the airflow increases. Lack anatomical verification of areas of stenosis. Change in airway outcome not validated against OSA measurement.

*All measurements rounded-up to one decimal.
Abbreviations, in addition to those in table 2.2.3: *MMA*: maxillary-mandibular advancement; *GTA*: genial tubercle advancement; *GGA*: genioglossus advancement; *CFD*: computational fluid dynamics; *REM*: Rapid eye movement; *O2sat*: oxygen saturation; *O2desat* : oxygen desaturation; *OxHm*: oxygenated haemoglobin; *H-palate*: hard palate; *S-palate*: soft palate; *C3Cs*: cross section at 3rd cervical vertebra; *Subj*: subject; *T0-T1*: from baseline to after treatment

Imaging with CBCT

In five[23-27] studies, OSA subjected were imaged with CBCT in the seated/awake position twice; pre and post-surgically or with/without appliance. AbiRamia et al[28] imaged their OSA subjects in the supine/awake position. Schendel et al[29] failed to report their CBCT imaging protocol. Generally, most of the included studies used a large field of view (from 13 to 23 cm) and voxel size from 0.25 to 0.4 mm. The scanning time varied significantly according to the CBCT machine used. In general, the airway region of interest extended from the most inferior-anterior point of cervical vertebra C3 inferiorly to the mid-soft palate or the level of hard palate/posterior nasal spine, superiorly, table 2.2.5.

Table2.2.5: Airway region of interest (ROI) segmented from CBCT images

Study	**Superior limit**	**Inferior limit**	**Comments**
AbiRamia et al[28] El et al[25] Huynh et al[23]	PNS	Anterior-inferior point of C3	-
Haskell et al[26]	Edge of soft palate	Tip of epiglottis	Soft tissue landmarks
Singh et al[27]	Posterior nasal aperture	Hyoid bone	
Schendel and Hatcher[24]	Mid-soft palate*	Base of hyoid*	3D rendering was beyond the ROI.
Schendel et al[29]	PNS*	Anterior-inferior point of C3*	3D rendering was beyond the ROI.
*Data not clearly stated in the study, however could be extracted from the images provided. Abbreviations: PNS: posterior nasal spine; C3: third cervical vertebra			

Data analysis

Detailed analyses of all articles included in this review are summarized in tables 2.2.3 and 2.2.4. There were three articles[26-28] that studies the use of appliance therapy (table 2.2.3) and the remainder four articles[23-25, 29] studied the effects of surgical therapy namely MMA (maxillary-mandibular advancement) with or without GTA (genial tubercle advancement), table

2.2.4. The follow-up period was reported in five articles[23, 25, 27-29] and varied from 1.6-10 months. None of the authors of these articles included a control group, randomly selected their subjects, or had large sample sizes. Overall, there are a total of 50 adults with OSA; 22 females and 28 males in their fourth-fifth decades of life. Of these subjects, only 7 had surgery. The body mass index BMI was reported in only two studies[25, 28] and was reported to be less than 27 indicating non-obesity.

The diagnosis of OSA was confirmed for all subjects pre-treatment using polysomnography (PSG) except for the ones reported by Huynh et al[23]. The severity of the OSA ranged from mild to severe. Post-treatment PSG was completed only by El et al[25] and Schendel et al[29] which represented just 2 surgery subjects. Pre and post-treatment sleep questionnaire was completed by El et al[25] only and Singh et al[27] reported post treatment home-based sleep test on his single subject treated with a dental appliance. Huynh et al[23] reported "history of OSA" in their inclusion criteria, but did not provide diagnostic evidence to support the diagnosis.

All articles included in this review analysed the orophayngeal (OP) with or without partial nasopharyngeal (NP) airway. Airway parameters measured were one or more of: linear, cross-sectional area, or volume except for one CFD (computational fluid dynamics) study by Huynh et al[23] where airway function was assessed by measuring total pressure drop and airway resistance at three different airflows. The changes in airway dimensions with treatment are summarized in tables 2.2.3 and 2.2.4.

2.2.4 Discussion

The ultimate goal in the treatment of SDB/OSA is to decrease the associated morbidity and mortality. The guidelines for successful treatment vary widely from achieving an Apnea-Hypopnea Index AHI of <10 to achieving at least a 50% reduction in the AHI.[4]

Quality and research bias

Since all seven articles analysed in this review were either small case series or single case reports, they had evidence levels of 4 or 5.[30] The fundamental disadvantages of such study designs pertain to the unknown changes in the upper airways in subjects who are untreated or received an alternate form of therapy. Accordingly, a quantitative/meta-analysis of this systematic review was not attainable.

Using the customized tool of bias evaluation, high risk of bias was found in all articles; mostly selection and detection/measurement bias. High selection bias can be explained by the lack of controls, small sample size, inadequate recruitment of the test group and lack of its randomization. OSA patient selection was not adequate in the study by Huynh et al[23] as they failed to report PSG findings to establish the diagnosis of OSA in their small case series. Detection/measurement bias can be attributed mainly to the lack of blinding the assessor/examiner to the intervention, uncontrolled confounding factors such as BMI or skeletal form, non-reliable measures to assess intervention and/or the outcome. Although the remainder six studies[24-29] confirmed the diagnosis and severity of OSA before treatment using PSG, only El et al[25] and Schendel et al[29] reported PSG findings after surgical treatment. Singh et al[27] failed to used consistent assessment of OSA by using home-based sleep test post-treatment. To answer the question whether CBCT is an objective tool to assess treatment outcomes in SDB/OSA subjects, it must be validated against another methodology known to clinically assess treatment outcome.

In the realm of SDB/OSA, the primary standard to assess the existence and severity of OSA is PSG, by means of AHI.[5, 7] Examples of other tools that have been used, not necessarily validated, to assess the level/stage of OSA are home-based sleep study, acoustic reflectometry, pressure catheters, sleep nasoendoscopy, or QOL/sleep questionnaires. Only two studies, with just 2 surgery patients, reported post treatment PSG. Only one study, representing just one patient treated with a dental appliance, used a home-based study post treatment. Unfortunately, since very few subjects who have been evaluated with CBCT also had post treatment PSG, the usefulness of airway dimensional changes as a tool to assess surgical and dental treatment outcomes cannot be adequately determined.

The reliability of the outcome measurement (i.e. airway dimensions from CBCT) would be ideally tested by inter and /or intra-examiner agreement using ICC (intra-class correlation coefficient) to ensure its reproducibility. This was reported in two studies[26, 28]only. Analysis/interpretation bias was found in studies[26, 28] that reported significance based on p values more than 0.05 or ignored the value of correlation coefficient (R^2). Performance bias was detected when the authors[25-27, 29] did not rule-out the impact of previous or concurrent intervention on the upper airway.

CBCT protocol

The CBCT protocol was fairly heterogeneous relative to resolution, CBCT brand, and patient positioning thereby, potentially affecting the accuracy of 2D and 3D measurements. It has been shown that airway dimensions change according to head posture. In a cephalometric study of OSA subjects, it was evident that when head position changed from upright to supine, the velopharynx significantly reduced in the anteroposterior dimension and was the narrowest site in both body positions.[31] This can be attributed to gravity and relaxation of the soft palate, tongue

and change in hyoid bone position.[32] Theoretically, this means that patients must be imaged in the supine position however a "stationary" supine position does not truly reflect the "shifting/changeable" positions during sleep. A major factor to changes in airway dimension is related to the state of sleep vs. awake. Upon the transition from awake to non-rapid eye movement (NREM) sleep, the diaphragm and muscles of the upper airway show reductions in activity with hypoventilation and two to five folds increase in upper airway resistance.[33] In rapid eye movement sleep, these parameters start to reverse to levels above those noted in NREM sleep or quiet wakefulness. Trudo et al[34] studied the state dependence of upper airway in a normal subject using 3D MRI reconstructions over several respiratory cycles during in sleep and wakefulness. The 3D images of the pharyngeal airway during NREM sleep showed medio-lateral reduction in the retro-palatal area and not in the retro-glossal region. [33, 34] This demonstrates that the upper airway does not behave as a homogeneous tube due to sleep and its effects on the pharyngeal muscle tone.[33, 34]

It is difficult to understand the pathophysiology of the airway in the awake patient, whether supine or in the upright position.[35] Since patients are awake during the CBCT scan, imaging in the supine position is not necessarily ideal since sleeping conditions are not simulated.

Most of the studies included in this review analysed similar airway region of interest (OP with part of the NP), few variations exist (table 2.2.5). The studies by Schendel and Hatcher[24] and Schendel et al[29] failed to clearly state the borders of the airway analysed, however it was possible to extract this data from the images provided. A note, however, is made of the "over-flow" of the 3D rendering beyond the borders marked on the 2D image. As such, the changes in airway parameters in this review were provided as % in difference/change, when possible.

The most common airway parameters measured were total volume and minimum cross-sectional (MinCS) area, followed by area and linear measurement (Lateral and antero-posterior dimensions) at certain anatomical locations (e.g. C2, C3, Hard or soft palate).

Data analysis

There are a total of 50 adults with OSA. The body mass index, BMI, was reported in only two studies[25, 28] and was less than 27; indicating non-obesity. Indeed, it has been documented that obesity (mild through severe) is on the rise and is associated with an increased prevalence of OSA in the general population.[36, 37] The design of most articles included in this systematic review, i.e. case reports, does not allow studying the effect of BMI on OSA treatment outcome or to control for it.

Appliance therapy[26-28]

All three studies[26-28] analysed subjects with mild to moderate OSA and included the oropharyngeal airway with or without part of the nasopharyngeal airway.

AbiRamia et al[28] utilized modified Twin Block appliance in 16 patients to advance the mandible to 75% of maximum protrusion. This was, however, stated vaguely without detailed reporting of the exact advancement per subject. The appliance was removable and all patients were instructed to wear the appliance at night. Each subject was imaged at the end of treatment period twice; with and without the appliance. Their reasoning for this was to maintain ideal head position and avoid changes in BMI or airway parameters due to climate change. AbiRamia et al[28] found that after 7 months of appliance therapy the total airway volume increases by 1.1±0.2 cm^3 (15 ±6%) when the appliance is in place. They reported their finding to be statistically significant however the *p* value of 0.0494 (i.e. almost 0.05) would be considered weak evidence of a

significant difference. Furthermore, these measurements were not validated clinically by evaluating the change in OSA severity, if any, at the end of treatment period.

Haskell et al[26] analysed the use of a mandibular advancement device; removable Herbst appliance in 26 OSA subjects over unknown period of therapy. The appliance was titrated by the patient gradual adjustment of the pistons (i.e. part of the appliance) to a more forward position. Each subject was imaged twice; with and without the appliance. The mean horizontal movement of the mandible, measured as the distance from antero-superior aspect of C3 to pogonion, was 4±3.6 mm. The large standard deviation indicates variability in the amount of mandibular horizontal movement among patients in their study. The authors quantified the increase in the total volume of the oropharynx to be 2.8±4.4 cm^3. They also quantified area and linear measurements at three cross sectional levels; minimum, largest, and at the level of cervical vertebra C2 (axis). The MinCS area changed by 0.4±0.9cm^2, the AP dimension increased by 0.1cm, and the increase in Lat dimension ranged between 0.3 and 0.4 cm. The authors found that the largest changes occurred more in the lateral dimension rather than antero-posteriorly, and was located at the level of C2 indicating that the upper airway acquired more of an elliptical shape, in cross-section. The data provided did not allow calculation of percentage change. While these measurements appeared to be statistically significant (by means of Z-scores between -1 and 1; suggesting small P-value), it was not validated clinically by evaluating the level of OSA at the end of treatment period.

Singh et al[27] reported the use of new maxillary appliance DNA (Day-night appliance) in one subject over 10 months. The customized removable maxillary appliance allowed the patient to turn the midline expansion screw if the appliance became loose. The patient was instructed to wear the maxillary appliance during the day and night for a minimum of 12-16 hours. The screw

was advanced twice weekly at 0.25mm on each turn. The authors reported an increase in the inter-molar width by 14.71% (5mm). However, failed to describe the details of the mandibular appliance and reported a forward movement by 2.9mm according to the jaw-tracking data. In terms of airway changes, the authors reported an increase in the total volume by 9.1 cm^3 (71%). Albeit, the patient was concurrently using CPAP and mandibular appliance and the subjective improvement in breathing cannot be attributed solely to the use of the maxillary appliance. In addition, the subject did not complete the same pre-treatment OSA test, a PSG, after treatment. Rather, the patient completed a home-based sleep test (Type IV monitoring device). Although home sleep tests are advantageous in terms of duration and cost, the literature lacks high-quality studies to clarify the diagnostic accuracy of home-based sleep tests.[38, 39]

Surgical treatment[23-25, 29]

Three[24, 25, 29] out of the four studies with surgical intervention analysed subjects with moderate to severe OSA; Huynh et al[23] failed to report the severity of OSA pre and post-surgically. All studies[23-25, 29] included the oropharyngeal airway with or without part of the nasopharyngeal airway and performed MMA with or without GTA.

El et al[25] analysed the upper airway of one OSA subject 6 months after MMA with GTA surgery and reported advancement of 7mm for the mandible and 6mm for maxilla. The authors quantified the increase in the oropharyngeal volume, by 6.5 cm^3 (82%) and MinCS area, by 1.2 cm^2 (269%). Linear measurements were reported at three cross sectional levels; minimum constriction at hard palate, minimum constriction at soft palate, and at the level of cervical vertebra C3. The increase in AP and Lat dimensions ranged from 0.1 to 0.6 cm (7%-317%) and 0.8 to 1.4 cm (55%-95%), respectively (largest change was at the level of soft palate). The

authors found that the largest changes occurred more in the lateral dimension rather than antero-posteriorly indicating that the oropharynx acquired more of an elliptical shape, in cross-section. While these measurements appeared to be clinically significant by means of 27.0 drop in the AHI score (from severe to mild OSA), the study lacks statistical power; n=1.

Schendel and Hatcher[24] reported the effects of 10 mm MMA with GTA and genioglossus advancement on upper airway in one subject with moderate OSA after unknown time of follow-up. The authors report an increase in the MinCS area by 1.1 cm^2 (1598%) however, it was not validated clinically by means of PSG test.

Schendel et al[29], on the other hand, obtained pre and post-surgical PSG testing for their subject and reported 12mm horizontal advancement with MMA plus GTA. The authors quantified the increase in the upper airway volume, by 9.7 cm^3 (89%), and in the MinCS area, by 0.1 cm^2 (21%). While these measurements appeared to be clinically significant by means of 16 to 49.4 drop in the AHI score (from moderate/severe to mild OSA), the study lacks statistical power; n=1.

The study by Huynh et al[23] represents the only upper airway functional analysis of four OSA MMA surgery subjects by means of computational fluid dynamics, CFD. CFD provides airway assessment beyond anatomical changes; it better reflects how air changes (velocity, pressure, resistance…etc) as it flows through the nose to the lungs.[40, 41] Although this study did not report dimensional airway changes, the authors used CBCT generated 3D airway models for computer simulation of airflow pre and post-surgery. Airflow was simulated at 340, 400, and 460 ml/s. The changes in hydraulic diameter and Reynolds number along the pharyngeal airway as well as the contours of Eddy viscosity coefficient and relative pressure were plotted. The total

airway pressure drop and airway resistance changes after surgery were quantified and reported. Reynolds number is a dimensionless number used to characterize different types of fluid flow; the higher the Reynolds number the more turbulent the flow.[23] The eddy viscosity coefficient (a combination of turbulent production and diffusion) decreases in areas with reduced turbulence.[23] After MMA surgery, three out of four OSA subjects showed an overall increase in hydraulic diameter and perimeter, decrease in the Reynolds number and eddy viscosity coefficient. Collectively, the effect was a decrease in total airway pressure and airway resistance (over 90% reduction) and the respiratory force airflow tends to be more laminar, i.e. less turbulent, in nature. As flow speed simulation was increased, the amount of drop in total airway pressure and airway resistance increased. Conversely, the remainder subject showed opposite results. The authors speculate it is due to smaller amounts of MMA, smaller changes in hydraulic diameter and Reynolds number behaviour throughout the pharyngeal passage. The authors suggest it could be a pharyngeal shape/geometry issue that may not benefit from MMA surgery. Computational fluid dynamics approach to study airway function and correlation with anatomical changes post-treatment treatments is promising and worthy of additional research.

Shortcomings of this systematic review are related to:

- The fact that all studies included were case reports or small case series with evidence levels 4-5 and high risk of bias.
- The quality of CBCT images, as a product of acquisition protocol, may have had an impact on the accuracy of airway measurements.
- Lack of clinical validation/correlation of CBCT airway changes, except for two studies [25, 29].

Conclusions

It is clear that the literature lacks evidence pertaining to the use of CBCT to assess treatment outcomes in the SDB/OSA population. However, the available published studies provide evidence of utilizing CBCT to measure anatomic airway changes with surgical and dental appliance treatment for OSA.

Accordingly, it can be concluded that CBCT may emerge as an objective tool to anatomically and functionally assess SDB/OSA treatment outcomes. High quality-evidence level studies, with statistically appropriate sample sizes, and cross-validated clinically are needed, however, to determine the role of CBCT to assess of treatment outcome.

2.2.5 References

1. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med.* 1993;328:1230-1235.

2. Ioachimescu OC, Collop NA. Sleep-disordered breathing. *Neurol Clin.* 2012;30:1095-1136.

3. Jackman AR, Biggs SN, Walter LM, et al. Sleep-disordered breathing in preschool children is associated with behavioral, but not cognitive, impairments. *Sleep Med.* 2012.

4. Conley RS. Evidence for dental and dental specialty treatment of obstructive sleep apnoea. part 1: The adult OSA patient and part 2: The paediatric and adolescent patient. *J Oral Rehabil.* 2011;38:136-156.

5. Lumeng JC, Chervin RD. Epidemiology of pediatric obstructive sleep apnea. *Proceedings of the American Thoracic Society.* 2008;5:242-252.

6. Bhattacharjee R, Kheirandish-Gozal L, Spruyt K, et al. Adenotonsillectomy outcomes in treatment of obstructive sleep apnea in children: A multicenter retrospective study. *American Journal of Respiratory and Critical Care Medicine.* 2010;182:676-683.

7. Punjabi NM. The epidemiology of adult obstructive sleep apnea. *Proceedings of the American Thoracic Society.* 2008;5:136-143.

8. Young T. Rationale, design, and findings from the wisconsin sleep cohort study: Toward understanding the total societal burden of sleep-disordered breathing. *Sleep Medicine Clinics.* 2009;4:37-46.

9. Hoffstein V. Review of oral appliances for treatment of sleep-disordered breathing. *Sleep and Breathing.* 2007;11:1-22.

10. Chen H, Lowe AA, Strauss AM, et al. Dental changes evaluated with a 3D computer-assisted model analysis after long-term tongue retaining device wear in OSA patients. *Sleep and Breathing.* 2008;12:169-178.

11. Strauss RA, Burgoyne CC. Diagnostic imaging and sleep medicine. *Dent Clin North Am.* 2008;52:891-915.

12. Hatcher DC. Cone beam computed tomography: Craniofacial and airway analysis. *Sleep Medicine Clinics.* 2010;5:59-70.

13. Kim JH, Guilleminault C. The nasomaxillary complex, the mandible, and sleep-disordered breathing. *Sleep and Breathing.* 2011;15:185-193.

14. Shi H, Scarfe W, Farman A. Upper airway segmentation and dimensions estimation from cone-beam CT image datasets. *Int J CARS.* 2006;1:177-186.

15. Ogawa T, Enciso R, Shintaku WH, Clark GT. Evaluation of cross-section airway configuration of obstructive sleep apnea. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2007;103:102-108.

16. Georgalas C, Garas G, Hadjihannas E, Oostra A. Assessment of obstruction level and selection of patients for obstructive sleep apnoea surgery: An evidence-based approach. *J Laryngol Otol.* 2010;124:1-9.

17. Choi J-, Hur Y-, Lee J-, Clark GT. Effects of mandibular advancement on upper airway dimension and collapsibility in patients with obstructive sleep apnea using dynamic upper airway imaging during sleep. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontology.* 2010;109:712-719.

18. 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;15:63-69.

19. Aboudara CA, Hatcher D, Nielsen IL, Miller A. A three-dimensional evaluation of the upper airway in adolescents. *Orthodontics & craniofacial research.* 2003;6 Suppl 1:173-175.

20. Hatcher DC. Cone beam computed tomography: Craniofacial and airway analysis. *Dent Clin North Am.* 2012;56:343-357.

21. Levendowski DJ, Morgan T, Montague J, Melzer V, Berka C, Westbrook PR. Prevalence of probable obstructive sleep apnea risk and severity in a population of dental patients. *Sleep and Breathing.* 2008;12:303-309.

22. Viswanathan M, Ansari M, Berkman N, et al. Assessing the risk of bias of individual studies in systematic reviews of health care interventions. *Agency for Healthcare Research and Quality Methods Guide for Comparative Effectiveness Reviews.* 2012;AHRQ Publication No. 12-EHC047-EF.

23. Huynh J, Kim D, McQuilling M. Pharyngeal airflow analysis in obstructive sleep apnea patients pre- and post-maxillomandibular advancement surgery. *J of fluids Eng.* 2009;131:091101-091111.

24. Schendel SA, Hatcher D. Automated 3-dimensional airway analysis from cone-beam computed tomography data. *Journal of Oral and Maxillofacial Surgery.* 2010;68:696-701.

25. El AS, El H, Palomo JM, Baur DA. A 3-dimensional airway analysis of an obstructive sleep apnea surgical correction with cone beam computed tomography. *Journal of Oral and Maxillofacial Surgery.* 2011;69:2424-2436.

26. Haskell JA, McCrillis J, Haskell BS, Scheetz JP, Scarfe WC, Farman AG. Effects of mandibular advancement device (MAD) on airway dimensions assessed with cone-beam computed tomography. *Semin Orthod.* 2009;15:132-158.

27. Singh GD, Wendling S, Chandrashekhar R. Midfacial development in adult obstructive sleep apnea. *Dent Today.* 2011;30:124-127.

28. Abi-Ramia LBP, Carvalho FAR, Coscarelli CT, de Oliveira Almeida MA. Increase in upper airway volume in patients with obstructive sleep apnea using a mandibular advancement device. *Dental Press Journal of Orthodontics.* 2010;15:166-171.

29. Schendel S, Powell N, Jacobson R. Maxillary, mandibular, and chin advancement: Treatment planning based on airway anatomy in obstructive sleep apnea. *Journal of Oral and Maxillofacial Surgery.* 2011;69:663-676.

30. Sharma S. Levels of evidence. *Evidence-Based Eye Care.* 1999;1:5-6.

31. Tsuiki S, Almeida FR, Bhalla PS, Lowe AA, Fleetham JA. Supine-dependent changes in upper airway size in awake obstructive sleep apnea patients. *Sleep and Breathing.* 2003;7:43-50.

32. Battagel JM, Johal A, Smith A-, Kotecha B. Postural variation in oropharyngeal dimensions in subjects with sleep disordered breathing: A cephalometric study. *Eur J Orthod.* 2002;24:263-276.

33. Dempsey JA, Veasey SC, Morgan BJ, O'Donnell CP. Pathophysiology of sleep apnea. *Physiol Rev.* 2010;90:47-112.

34. Trudo FJ, Gefter WB, Welch KC, Gupta KB, Maislin G, Schwab RJ. State-related changes in upper airway caliber and surrounding soft- tissue structures in normal subjects. *American Journal of Respiratory and Critical Care Medicine.* 1998;158:1259-1270.

35. Sittitavornwong S, Waite PD. Imaging the upper airway in patients with sleep disordered breathing. *Oral and Maxillofacial Surgery Clinics of North America.* 2009;21:389-402.

36. Schwartz A, Patil S, Laffan A, Polotsky V, Schneider H, Smith P. Obesity and obstructive sleep apnea: Pathogenic mechanisms and therapeutic approaches. *Proc Am Thorac Soc.* 2008;5:185-192.

37. Knutson KL, Zhao X, Mattingly M, Galli G, Cizza G. Predictors of sleep-disordered breathing in obese adults who are chronic short sleepers. *Sleep Med.* 2012;13:484-489. doi:10.1016/j.sleep.2011.11.009.

38. Whittle A, Finch SP, Mortimore I, MacKay T, Douglas N. Use of home sleep studies for diagnosis of the sleep apnoea/hypopnoea syndrome. *Thorax.* 1997;52:1068-1073.

39. Flemons W, Littner M, Rowley J, et al. Home diagnosis of sleep apnea: A systematic review of the literature. an evidence review cosponsored by the american academy of sleep medicine, the american college of chest physicians, and the american thoracic society. *Chest.* 2003;124:1543-79.

40. Vos W, De Backer J, Devolder A, et al. Correlation between severity of sleep apnea and upper airway morphology based on advanced anatomical and functional imaging. *J Biomech.* 2007;40:2207-2213.

41. Sung S-, Jeong S-, Yu Y-, Hwang C-, Pae E-. Customized three-dimensional computational fluid dynamics simulation of the upper airway of obstructive sleep apnea. *Angle Orthod.* 2006;76:791-799.

Chapter 3

Improving segmentation and 3D analysis of upper airway CBCT images: pilot studies

3.1 Topical contrast agents to improve soft-tissue contrast in the upper airway using cone beam CT: a pilot study

3.2 Risk Assessment of Sleeping Disorder Breathing based on Upper Airway Centerline Evaluation

3.1 Topical contrast agents to improve soft-tissue contrast in the upper airway using cone beam CT: a pilot study*

N Alsufyani, M. Noga, W. Finlay, P. Major

*Published in Dentomaxillofacial Radiology 2013; 42: 20130022.

Preface

This research project, of which this thesis is a part, is an original work by Noura Alsufyani and received research ethics approval from the University of Alberta Research Ethics Board, Project Name "Topical contrast agents in the upper airway to improve signal to noise ratio in Cone Beam CT images: A pilot study", Pro00030422, September 20, 2012.

3.1 Topical contrast agents to improve soft-tissue contrast in the upper airway using cone beam CT: a pilot study

Abstract

Objective: To explore the topical use of radiographic contrast agents to enhance soft tissue contrast on cone beam computed tomography (CBCT) images. **Methods:** Different barium sulfate concentrations were first tested using airway phantom. Different methods of barium sulfate application (nasal drops, syringe, spray, and sinus wash) were then tested for four volunteers and nebulized iodine was tested in one volunteer. CBCT images were performed and then assessed subjectively by two examiners for contrast agent uniformity and lack of streak artifact. **Results:** 25% barium sulfate presented adequate viscosity and radio-density. Barium sulfate administered via nasal drops and sprays showed non-uniform collection at the nostrils, along the inferior and/or middle nasal meatuses, and posterior nasal choana. The syringe and sinus wash showed similar results with larger volumes collecting in the naso-oropharynx. Nebulized iodine failed to distribute into the nasal cavity and scarcely collected at the nostrils. **Conclusion:** All methods of nasal application failed to adequately reach or uniformly coat the nasal cavity beyond the inferior nasal meatuses. Key factors to consider for optimum topical radiographic contrast in the nasal airway are particle size, flow velocity, and radiopacity.

3.1.1 Introduction

Upper airway analysis has gained considerable attention in the medical and dental fields, especially in breathing disorders such as obstructive sleep apnea. Three-dimensional (3D) models of the upper airway segmented from Cone-beam computed tomography (CBCT) scans are emerging as means to visualize and assess the upper airway. Segmentation (manual, automatic or semi-automatic) refers to the extraction of structural information of particular interest from surrounding images. This analysis tool is essential because it defines the contours and boundaries of anatomy or pathology for visualization or characterization.[1]

Although CBCT provides less radiation compared to multi-detector CT (MDCT), CBCT presents with lower signal to noise ratio (SNR). The larger amounts of scattered radiation from the x-ray source in CBCT enhance noise in the reconstructed images, affect the low-contrast detectability, and thus may influence image quality and tissue segmentation accuracy.[2] Adding to the difficulty is the complex anatomy of the nasal airway which will affect boundary definition, gray-level thresholding, accuracy of 3D model, and any resultant quantitative analysis.[3]

Contrast agents are employed by many imaging modalities and can easily improve SNR by improving tissue contrast. Several studies used contrast agents (namely iodine) in the nasal and paranasal sinuses to assess nasal/sinus drug delivery using MDCT,[4, 5] nuclear medicine,[6-8] and CBCT.[9] To our knowledge, topical application of contrast agents in the upper airway as a method to enhance tissue contrast has not been investigated.

Therefore, the purpose of this pilot study was to explore the topical use of two contrast agents (Barium sulfate and iodine) to improve tissue contrast in the upper airway (nasal and pharyngeal parts).

3.1.2 Materials and Methods

Contrast agents: Different concentrations of barium sulfate suspension 105% w/v (Liquid Polibar Plus®, E-Z-EM Inc., Lake Success, NY) were tested. Then, different methods of application, including nasal drops, needle-less syringes, nasal spray, sinus wash, and nebulization, were tested, Figure 3.1.1).

Figure 3.1.1: Methods of contrast agent application. (A) For barium sulfate (left to right) syringe, drops, spray, and sinus wash). (B) For iodine: nasal adaptor for nebulization.

Because barium sulfate is insoluble and is partly cleared by mucociliary transport, expectoration and coughing, with the remainder removed by macrophages resulting in accumulation in the tracheobronchial lymph nodes and localized opacity for years.[10] Accordingly, barium sulfate was not nebulized. Instead, water-soluble-iodine 240 mg I/ml (Omnipaque iohexol 52%, GE Healthcare, Waukesha, WI) was nebulized, using the PARI SinuStar™ with nasal adaptor (PARI Respiratory Equipment Inc., Midlothian, VA), because it is water soluble and does not remain in the lung.

In vitro: An anthropomorphic airway phantom (Figure 3.1.2) was used to optimize the concentration of barium sulfate. The airway phantom included the pharyngeal, nasal and

paranasal airway from the level of frontal sinus superiorly to the hypo-pharynx inferiorly. It was built based on an MDCT scan of an adult subject by a rapid proto-typer using acrylic plastic with wax support material. The construction details of the model are described in the study by Storey-Bishoff et al.[11] Barium sulfate concentrations tested were 50%, 25%, and 12.5% by diluting with sterile water. Diluted barium sulfate (6 cc) was applied through each nasal aperture of the phantom in the supine position using a nasal syringe. Then, the phantom was moved and tilted to ensure distribution of the contrast agent. This was repeated for each concentration. After the application of each concentration of barium sulfate, the phantom was stabilized in a plastic cylinder such that it represented the human seated position, then scanned with the Classic iCAT CBCT scan (Imaging Sciences International, Hatfield, PA). CBCT protocol used a medium-large field of view (16 cm width x 13 cm height), 120 kVp, 24 mAs, 20 seconds scan time, and 0.3 mm voxel size. After each contrast application, the airway model was thoroughly washed with water and scanned again to ensure the lack of barium residue. The resultant images were subjectively and visually analyzed by two examiners (medical and oral & maxillofacial radiologists). Consensus between both examiners was reached to select the optimum barium sulfate concentration. Criteria for optimum concentration were absence of detrimental streak or beam hardening artifacts with complete uniform coating of the airway.

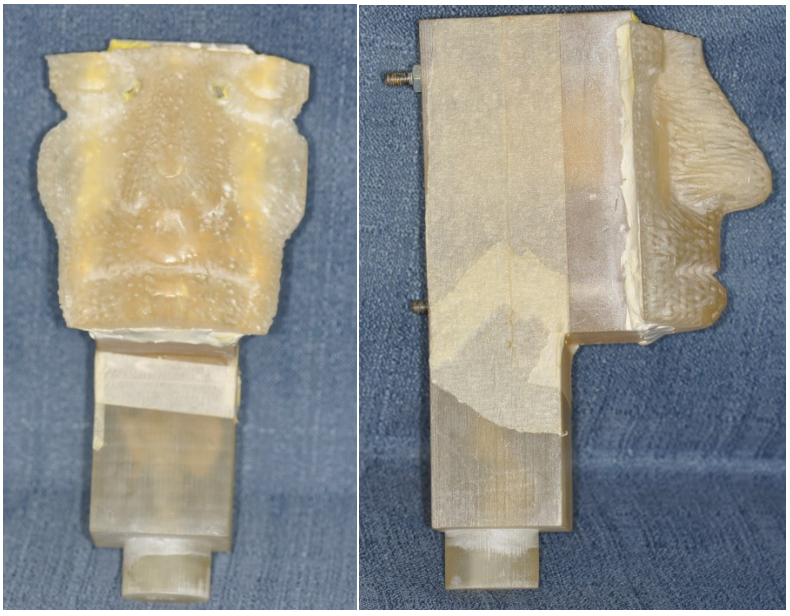


Figure 3.1.2: Anthropomorphic airway phantom. Left: frontal view, right: lateral view.

In vivo: Five healthy subjects were invited to volunteer in this pilot. Each volunteer received one method of contrast application as follows: four subjects received 6 cc of 25% barium sulfate per nostril (total 12 cc) using needle-less syringes, Salinex® nasal drops or spray (Sandoz Canada Inc., Boucherville, QC), or NeilMed® sinus wash (NeilMed® Pharmaceuticals Inc., Santa Rosa, CA). Each subject was asked to sniff after the administration of barium sulfate. One subject was asked to normally breathe 8 cc of nebulized water-soluble iodine. After the contrast application, a CBCT scan of the upper airway was completed for each participant using a small field of view (16 cm width x 8 cm height), 120 kVp, 24 mAs, 20 seconds scan time, and 0.3 voxel size. The resultant images were subjectively and visually analyzed by the same examiners. Consensus between both examiners was reached to select the optimum method of distribution i.e. uniform distribution throughout the nasal cavity (inferior, middle, superior meatuses, anterior naris/nostrils and posterior naris/choana).

3.1.3 Results

In vitro (barium sulfate concentration)

CBCT images of 50%, 25%, and 12.5% barium (6cc/nostril) are presented in Figure 3.1.3. 25% barium sulfate presented adequate viscosity and reasonable radio-density.

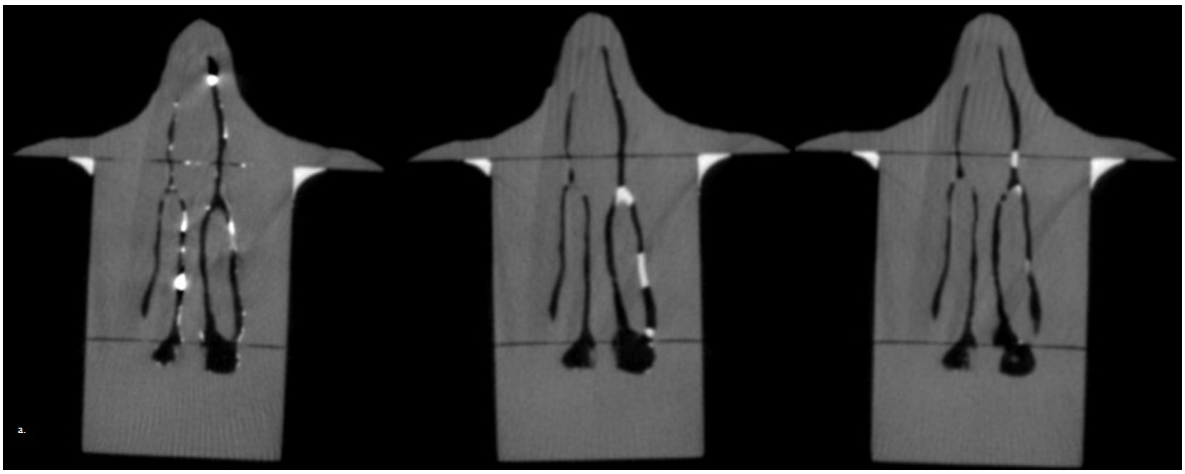


Figure 3.1.3: Barium sulfate concentrations using the airway phantom. CBCT axial images through the inferior nasal meatus with 50%, 25%, and 12.5% barium sulfate, from left to right.

In vivo (methods of application): None of the volunteers showed immediate or delayed reaction to the contrast agents used in this pilot. CBCT images of barium sulfate applied via nasal drops, spray, syringe, sinus wash, and nebulized iodine are presented in Figures 3.1.4. Barium sulfate inhomogenously collected at the nostrils and along the inferior and/or middle nasal meatuses, and posterior nasal choana. Nebulized iodine failed to distribute into the nasal cavity and scarcely collected at the nostrils.

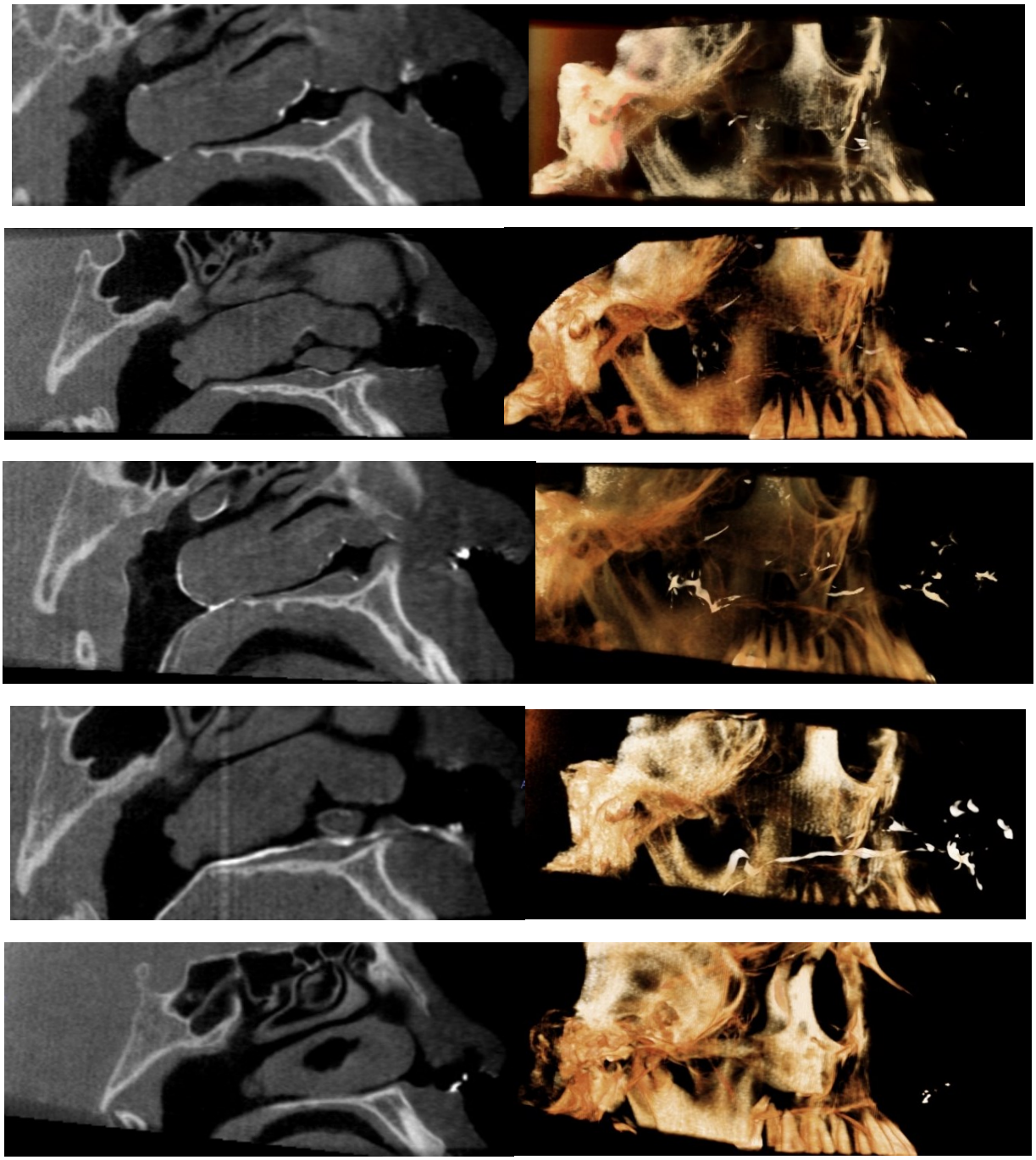


Figure 3.1.4: Sagittal (2D and 3D) CBCT images of the nasal cavity using different application methods of contrast. From top to bottom: using nasal drops, spray, syringe, sinus wash, and nebulization.

3.1.4 Discussion

Barium sulfate was chosen for this pilot because of its greater radiographic density compared to water soluble iodine contrast agents.[12] Due to its iso-osmolarity, barium sulfate can also give better mucosal coating and adherence as noted in sites of gastro-intestinal leakage.[12, 13]

The ideal barium sulfate/water mixture has yet to be developed. Key factors for this mixture are: radiopacity, concentration, and viscosity. Ideally, the contrast agent distributing along the upper airway would be of low-medium viscosity, to allow reasonable flow with even coating, and medium radiopacity, to avoid detrimental beam-hardening artifact; suggesting that medium-low concentration is preferred. Using the airway phantom, 50% barium sulfate was too radiopaque with evident beam hardening artifacts, Figure 3.1.3. However, it showed more areas of contrast adherence due to its higher viscosity. 25% and 12.5% barium sulfate were of acceptable radiopacity, i.e. no streaking or beam hardening, however less coating of the nasal cavity. 25% concentration was chosen due to larger amounts of contrast retention because most of the 12.5% contrast agent leaked through the phantom's hypopharynx.

In studies similar to this pilot, the amount of radiographic contrast used varied between 0.3 to 40 ml (Drops: 1.5 ml/naris,[9] Spray: 0.3-10 ml/naris,[5, 8, 9] Syringe: 40 ml/naris,[5, 8] and Sinus wash: 20 ml/naris).[4] The smaller end of the spectrum was likely selected to reflect typical volumes used in nasal medications, whereas the larger amounts (i.e. 40 ml) were used based on the recommendation that 50 ml could fill the average sinus.[9] For this pilot study, the authors chose to use 6 ml/naris of contrast agent to allow reasonable contrast distribution while reducing subject discomfort.

Using 6 cc/nostril of 25% for barium sulfate, all methods of application demonstrated non-uniform collection at the nostrils, along the inferior and/or middle nasal meatuses, and posterior nasal choana, Figure 3.1.4). However, syringe and sinus wash showed larger volumes collecting in the naso-oropharynx/dorsum of soft palate. These findings are in agreement with similar studies using iodine. However, Olson et al[4] and Snidvong et al[5] tested sinus delivery using iodine. Using spray and syringe or sinus wash and positive pressure irrigation (sniffing contrast from the palm of the hand), it was evident that most of the contrast agent drained through the nose or oropharynx with few streaks of contrast in the maxillary sinuses, inferior and middle meatuses of the nasal cavity.[4,5] Similarly, Rudman et al[9] found that iodine (via nasal spray and drops) variably collected along the anterior nasal vestibule, anterior-inferior meatus, and nasopahrynx. Senocak et al[14] used nasal spray and assessed iodine distribution in the nasal cavity over time by imaging with MDCT three times (three minutes apart). Iodine collected in the anterior nasal floor and inferior turbinate and with time, it reduced in volume and reached the posterior nose then nasopharynx in few subjects.[16] In these studies, the ultimate goal was local drug delivery to the sino-nasal cavity and the contrast agent was considered even if only a small droplet reached an anatomical area. As such, it was counted and quantified by means of volume or proportion. In this pilot, however, the aim was for the contrast agent not only to reach the superior anatomical areas of the nose, but also to uniformly coat their surfaces to enhance soft tissue contrast. Thus, the assessment was qualitative and subjective.

Nebulization delivers drugs to the bronchopulmonary system either through the oral or nasal cavities. The PARI SinusStar™ has a capacity of 6-8 cc with 0.180 ml/min output rate. Using the nasal adaptor, the time to nebulize 8 cc of full concentration iodine was around 11 minutes. Nebulized iodine failed to distribute into the nasal cavity and scarcely collected at the

nostrils, Figure 3.1.4. This was in agreement with Olson et al,[4] where 20 cc/naris of iodine was nebulized by delivering 10 cc in low flow then repeated by filling the chamber with 10 cc at high flow. It was reported that particle size < 5μm had higher deposition rate to the osteomeatal complex and maxillary sinus.[15] In this pilot, the quantity and quality (i.e. particle size) of iodine particles produced, reached, or bypassed the nasal cavity is unclear.

Based on the preliminary results of this pilot, two factors must be considered in delivering contrast agent to the upper airway: particle size and flow velocity. Computational simulation of particle deposition using validated airway casts or three dimensional airway models have been used to assess nasal drug delivery.[16, 17] Using these simulations, the optimum method of delivery and its impact on the physical properties of the contrast agent, including radioapcity, could be identified.

3.1.5 References

1. Sharma S, Sharma P. A novel technique of skeletonization for feature extraction in cadastral maps. *Int J Electron Comput Sci Eng* 2012; 1: 1057-1061.
2. Endo M, Tsunoo T, Nakamori N, Yoshida K. Effect of scattered radiation on image noise in cone beam CT. *Med Phys* 2001; 28: 469-474.
3. Alsufyani NA, Flores-Mir C, Major PW. Three-dimensional segmentation of the upper airway using cone beam CT: A systematic review. *Dentomaxillofac Radiol* 2012; 41: 276-284.
4. Olson DE, Rasgon BM, Hilsinger RL. Jr. Radiographic comparison of three methods for nasal saline irrigation. *Laryngoscope* 2002; 112: 1394-1398.
5. Snidvongs K, Chaowanapanja P, Aeumjaturapat S, Chusakul S, Praweswararat P. Does nasal irrigation enter paranasal sinuses in chronic rhinosinusitis? *Am J Rhinol* 2008; 22: 483-486.
6. Hwang PH, Woo RJ, Fong KJ. Intranasal deposition of nebulized saline: A radionuclide distribution study. *Am J Rhinol* 2006; 20: 255-261.
7. Hilton C, Wiedmann T, St Martin M, Humphrey B, Schleiffarth R, Rimell F. Differential deposition of aerosols in the maxillary sinus of human cadavers by particle size. *Am J Rhinol* 2008; 22: 395-398.
8. Wormald P, Cain T, Oates L, Hawke L, Wong I. A comparative study of three methods of nasal irrigation. *Laryngoscope* 2004; 114: 2224-2227.
9. Rudman KL, O'Brien EK, Leopold DA. Radiographic distribution of drops and sprays within the sinonasal cavities. *Am J Rhinol Allergy* 2011; 25: 94-97.
10. Buschmann C, Schulz F, Tsokos M. Fatal aspiration of barium sulfate. *Forensic Sci Med Pathol* 2011; 7: 63-64.
11. Storey-Bishoff J, Noga M, Finlay WH. Deposition of micrometer-sized aerosol particles in infant nasal airway replicas. *J Aerosol Sci* 2008; 39: 1055-1065.
12. Tanomkiat W, Galassi W. Barium sulfate as contrast medium for evaluation of postoperative anastomotic leaks. *Acta Radiol* 2000; 41: 482-485.
13. Swanson JO, Levine MS, Redfern RO, Rubesin SE. Usefulness of high-density barium for detection of leaks after esophagogastrectomy, total gastrectomy, and total laryngectom. *AJR Am J Roentgenol* 2003; 181 :415-420.
14. Senocak D, Senocak M, Bozan S. Sinonasal distribution of topically applied particles: Computerized tomographic detection and the effects of topical decongestion. *Otolaryngol Head Neck Surg* 2005; 133: 944-948.
15. St Martin MB, Hitzman CJ, Wiedmann TS, Rimell FL. Deposition of aerosolized particles in the maxillary sinuses before and after endoscopic sinus surgery. *Am J Rhinol* 2007; 21: 196-197.
16. Inthavong K, Ge Q, Se CM, Yang W, Tu JY. Simulation of sprayed particle deposition in a human nasal cavity including a nasal spray device. *J Aerosol Sci* 2011; 42: 100-113.
17. Liu Y, Matida EA, Johnson MR. Experimental measurements and computational modeling of aerosol deposition in the Carleton-Civic standardized human nasal cavity. *J Aerosol Sci* 2010; 41: 569-586.

3.2 Risk Assessment of Sleeping Disorder Breathing based on Upper Airway Centerline Evaluation*

Noura Alsufyani, Rui Shen, Irene Cheng, Paul Major

* Published, in part, in Proceedings SPIE 8670, Medical Imaging 2013: Computer-Aided Diagnosis, 86702M doi:10.1117/12.2006687

Preface

This project was a collaboration between the Departments of Computing Sciences and Dentistry at the University of Alberta. I was responsible for the data collection and contributed to manuscript composition. From the Computing Sciences, Rui Shen was responsible for concept formation, assisted with the data collection and analysis as well as the manuscript composition, Dr. Irene Cheng (from Computing Sciences) was a supervisory author and was involved with concept formation and manuscript composition. Dr. Paul Major is the supervising author to this thesis and was involved with concept formation and manuscript composition.

This research project, of which this thesis is a part, received research ethics approval from the University of Alberta Research Ethics Board, Project Name "Automatic Segmentation of the Upper Airway using Cone Beam Computed Tomography: A validation study", Pro00021181, March 16, 2011.

3.2 Risk Assessment of Sleeping Disorder Breathing based on Upper Airway Centerline Evaluation

ABSTRACT

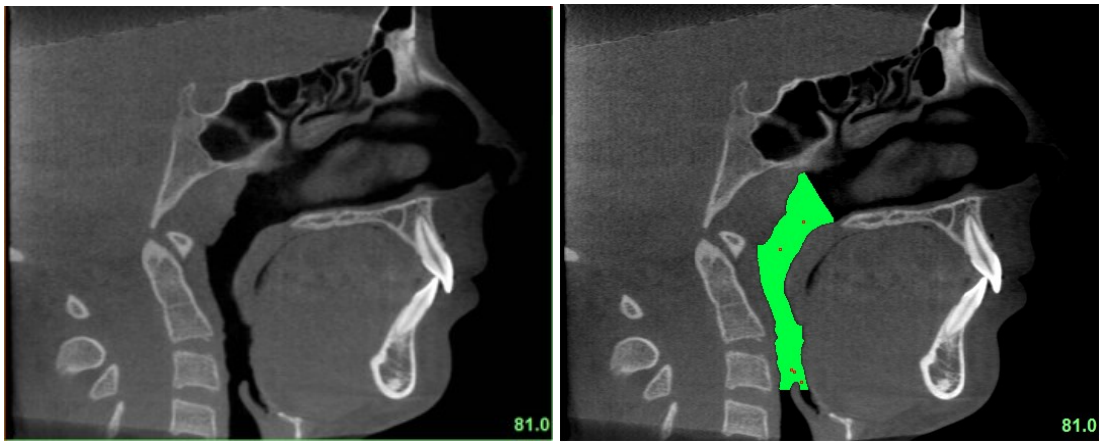
Cone-beam computed tomography (CBCT) is used to assess the location or cause of upper airway obstruction. To date, all studies analyzing the upper airway in subjects with Sleeping Disorder Breathing were based on linear, area, or volumetric measurements, which are global computations and can easily ignore local significance. Skeletonization was initially introduced as a 3D modeling technique by which representative medial points of a model are extracted to generate centerlines for evaluations. Although centerlines have been commonly used in guiding surgical procedures, the novelty lies in comparing its geometric properties before and after surgeries. We apply 3D data refinement, registration and projection steps to quantify and localize the geometric deviation in target airway regions. Through cross validation with corresponding subjects' therapy data, we expect to quantify the tolerance threshold beyond which reduced dimensions of the upper airway are not clinically significant. The ultimate goal is to utilize this threshold to identify patients at risk of complications. Preliminary results demonstrate the feasibility of our approach.

3.2.1 Introduction

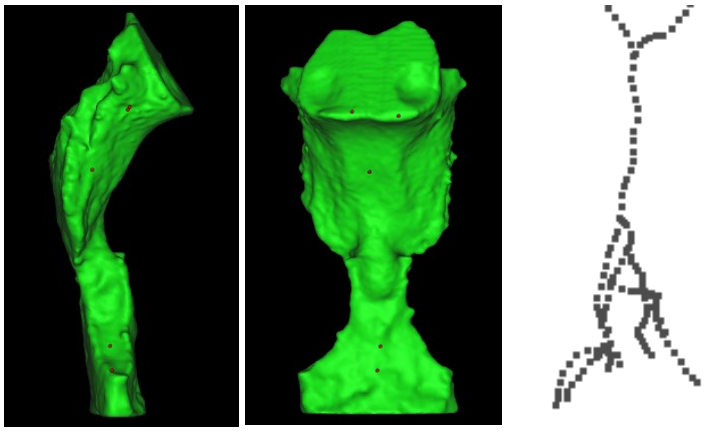
Obstruction of the upper airway often affects normal breathing and sleep-disordered breathing such as obstructive sleep apnea (OSA).[1] OSA is one of the most important breathing disorders in childhood affecting 2–3% of children with failure rates of surgical treatment as high as 54%.[2-7] Obstructions of the upper airway due to adenoid tissues which are further compressed when muscle tone is decreased during sleep are possible factors. As computer aided diagnosis (CAD) advances the ability to identify the location or cause of the airway obstruction continues to improve. Many researchers make use of the popular Cone-beam computed tomography (CBCT) devices to capture the head and neck and segment the upper airway for assessment.[9-12]

To date, all studies analyzing the upper airway in subjects with Sleeping Disorder Breathing were based on linear, area, or volumetric measurements.[1] However, Huynh et al pointed out that unfavourable condition in respiratory airflow after surgery was found and suggested it could be a shape or geometry issue.[13] Since 2D and volumetric measurements are based on global averaging, they are inadequate indicators. It would be more meaningful if changes in geometry and shape targeting local significance could be assessed in these airway models.

Skeletonization is a process to extract representative medial points of a model to generate centerlines for evaluations, Figure 3.2.1. Although centerlines have been commonly used in guiding surgical procedures[14], the novelty lies in comparing its geometric properties before and after surgeries.



(A) (B)



(C) (D) (E)

Figure 3.2.1: 3D segmentation of upper airway from CBCT. (A) Upper airway before segmentation (B) region of interest highlighted (C) 3D model generated, lateral view (D) 3D model frontal view (e) example of medial points "skeleton".

3.2.2 Methods

Two CBCT image sets were retrieved from Orthodontic Graduate clinic database at the University of Alberta. The images were acquired by the Classic iCAT CBCT scan (Imaging Sciences International, Hatfield, PA). CBCT protocol used a medium-large field of view (16 cm width x 13 cm height), 120 kVp, 24 mAs, and 0.3 mm voxel size. Using Mimics® software [Mimics 15.0, Materialise NV, Leuven, Belgium][15], the pharyngeal airway was segmented, from the inferior aspect of the third cervical vertebra (C3) inferiorly to the posterior nasal aperture superiorly, by adjusting the grey threshold on each 2D axial and/coronal slices. Then, a 3D model of the airway is reconstructed and saved in .STL format. The centerline was generated for each airway by using the *centerline* application in Mimics®, then post-surgery centerline was simulated using a deformation algorithm. The deviation between centerlines generated before and after surgery in the upper airway will be measured.

Seven anatomical markers for registration were used to register the pre- and simulated post-surgical models. These were: 1. sella; 2. clivus; 3. 2nd cervical vertebra; 4. 3rd cervical vertebra; 5. Tip of the nose; 6. left hamulus; 7. right hamulus, Figure 3.2.2.

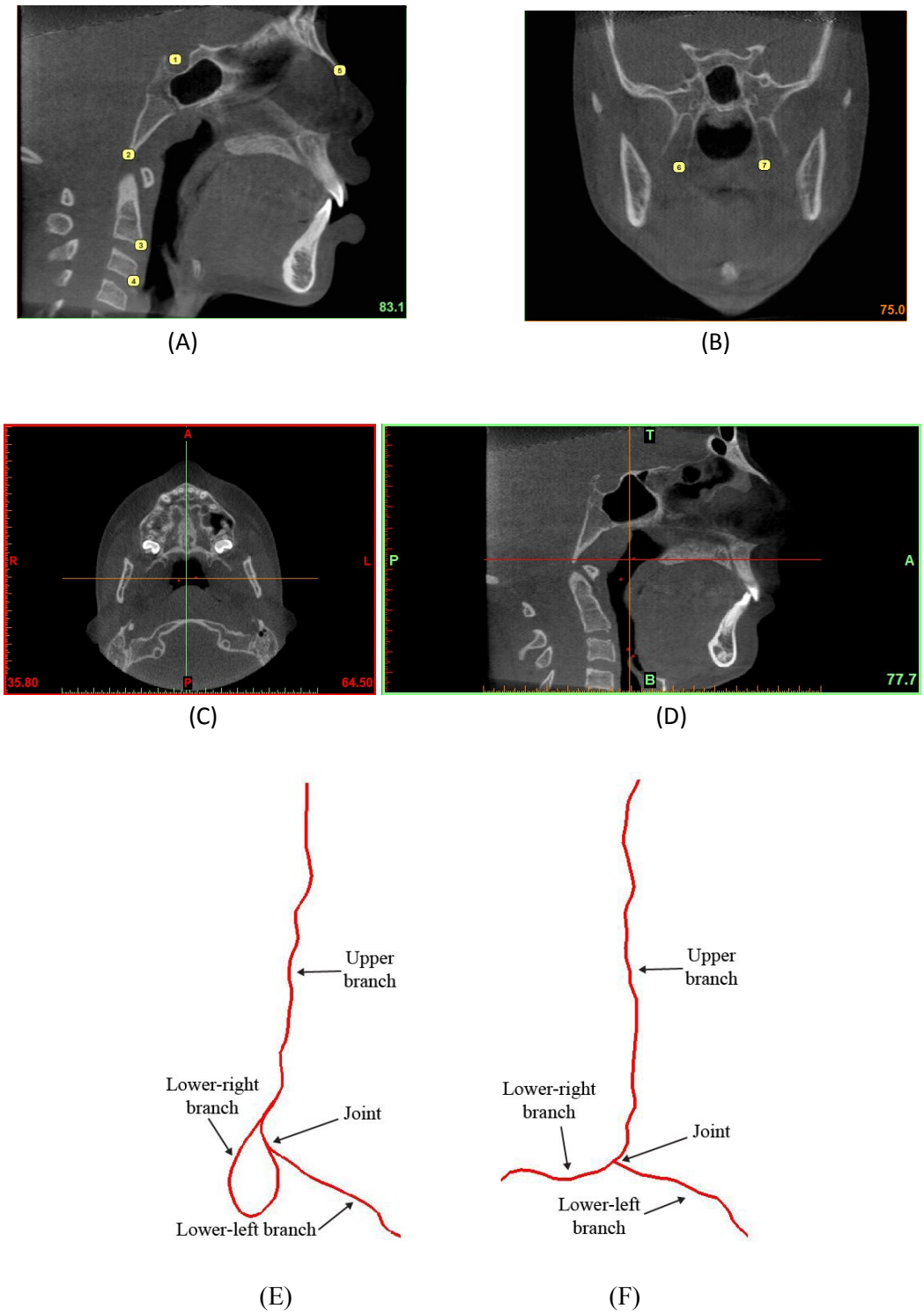


Figure 3.2.2: Registration and centerline formation. (A) Sagittal and (B) coronal CBCT images showing registration marks. (C) Axial and (D) sagittal CBCT images showing coordinate system. (E) and (F) Extracted pre-surgery centerlines for two subjects.

When setting up the coordinate system, the lower joint on the skeleton is defined as the one i) incident on three branches, i.e., having a node degree of three, ii) below registration marker C2, and iii) with the largest distance to C2 in the z-direction but with the smallest distance to C2 in the x-y plane. The coordinate system is shown in Figure 3.2.2 (C-D).

We first form the centerline segments from the medial points. Registration is performed by matching the lower joint, upper branch, as well as the lower right and left branches as shown in Figure 3.2.2 (E-F). The geometric deviation between the pre- and post-surgery centerlines is calculated in the target region, *i.e.*, upper branch in our current surgery simulation, following three steps. First, sampling is performed on the upper branch of the post-surgery centerline. *N* sample points are uniformly placed on the upper branch between its two end points, *i.e.* N=100. They are uniformly placed based on the z-coordinate. Second, sample projection is done on the pre-surgery centerline to find matching points. The process is illustrated in Figure 3.2.3 (A). In the last step, per-sample deviation between a sample and its projection is calculated as their Euclidean distance in the x-y plane.

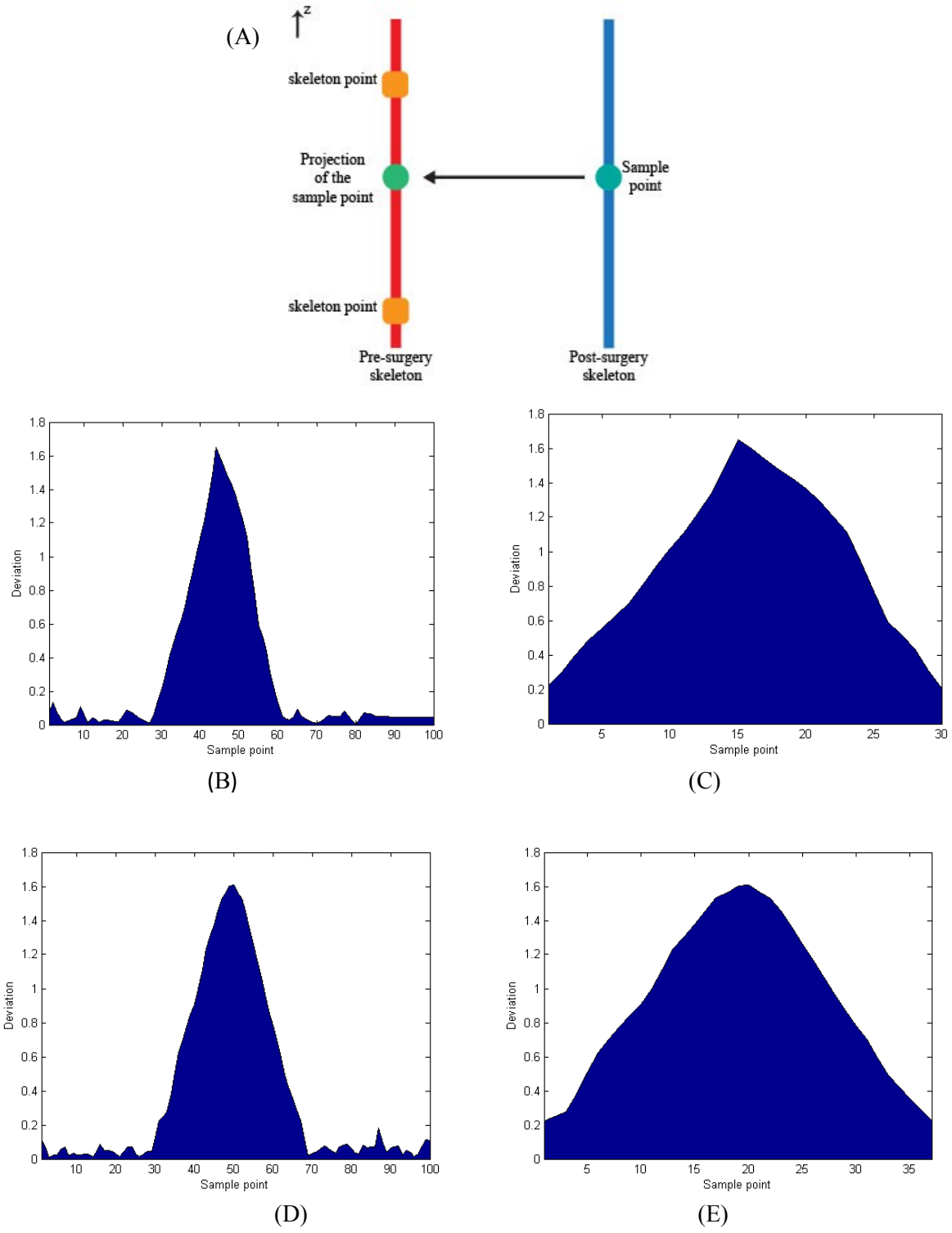


Figure 3.2.3: Centerline geometric deviation. (A) Sample projection on the pre-surgery centerline. (B) All 100 sample point deviations for subject 1, clinically significant when a threshold θ is set to -1. (C) 30 sample points selected for the same subject, clinically significant when a threshold θ is set to 0.2. (D) All 100 sample point deviations for subject 2, clinically significant when a threshold θ is set to -1. (E) 37 sample points selected for the same subject, clinically significant when a threshold θ is set to 0.2.

3.2.3 Results

The average, maximum, and minimum deviations are calculated. The average deviation is computed on samples whose deviations are above a threshold θ. We used two threshold values, -1 and 0.2 to control the filtering of insignificant deviations. For example, in subject 1 and 2 when θ= -1, all the samples are included. In this case, the average deviation, maximum deviation, and minimum deviation are:

(Subject 1) 0.309301, 1.64984, and 0.00453, respectively;

(Subject 2) 0.378014, 1.61043, and 0.00546, respectively.

When $\theta = 0.2$, the calculation includes 30 samples for subject 1 and 37 for subject 2, such that the average deviation, maximum deviation, and minimum deviation are:

(Subject 1) 0.920059, 1.64984, and 0.20103, respectively;

(Subject 2) 0.929027, 1.61043, and 0.222272, respectively.

Results for subject 1 and subject 2 are depicted in Figure 3.2.3 (B,E). By analyzing the shape of the histogram, local deformations in the target upper airway region can be determined. Significance of these deformations can be validated using clinical data and a predictive model, quantified by a risk threshold value, can eventually be developed.

Conclusion

Preliminary results demonstrate that it is beneficial to use our approach for objective and quantitative measurements of the airway changes. Although centerlines have commonly been used in guiding surgery, here centerline computation is applied to assess the upper airways. This method could ultimately be used to identify groups at risk of complications based on the geometry of their airway or estimate treatment success based on airway measurements. Our finding will introduce a new method to quantify changes in the upper airway in a meaningful way compared to the global averaging approach. It will demonstrate where and how different local upper airway sites deform and their correlation with surgical outcome. Through validation with surgical outcome, we expect to quantify the tolerance threshold beyond which reduced dimensions of the upper airway are not clinically significant. We will further validate our finding by increasing our subjects to 50 or more.

3.2.4 References

1. Alsufyani, N.A., Flores-Mir, C. and Major, P.W., Three-dimensional segmentation of the upper airway using cone beam CT: a systematic review. *Dentomaxillofacial Radiology*. 2012; 41, 276-284.

2. Lumeng J.C and Chervin R.D. Epidemiology of pediatric obstructive sleep apnea. *Proceedings of the American Thoracic Society.* 2008;5:242-252.

3. Bhattacharjee R, Kheirandish-Gozal L, Spruyt K, et al. Adenotonsillectomy outcomes in treatment of obstructive sleep apnea in children: A multicenter retrospective study. *American Journal of Respiratory and Critical Care Medicine.* 2010;182:676-683.

4. Costa D. J and Mitchell R., Adenotonsillectomy for obstructive sleep apnea in obese children: A meta-analysis. *Otolaryngology - Head and Neck Surgery.* 2009;140:455-460.

5. Friedman M, Wilson M, Lin H. and Chang H.. Updated systematic review of tonsillectomy and adenoidectomy for treatment of pediatric obstructive sleep apnea/hypopnea syndrome. *Otolaryngology - Head and Neck Surgery.* 2009;140:800-808.

6. Tait AR, Voepel-Lewis T, Burke C, Kostrzewa A and Lewis I., Incidence and risk factors for perioperative adverse respiratory events in children who are obese. *Anesthesiology.* 2008;108:375-380.

7. Fung E, Cave D, Witmans M, Gan K and El-Hakim H. Postoperative respiratory complications and recovery in obese children following adenotonsillectomy for sleep-disordered breathing: A case-control study. *Otolaryngology - Head and Neck Surgery.* 2010;142:898-905.

8. Shelton K.E., Woodson H, Gay S and Suratt P.M,. Pharyngeal fat in obstructive sleep apnea. *Am Rev Respir Dis.* 1993;148:462-466.

9. Hatcher D.C., Cone beam computed tomography: Craniofacial and airway analysis. *Sleep Medicine Clinics.* 2010;5:59-70.

10. McCrillis J.M., Haskell J and Haskell B.S, et al., Obstructive sleep apnea and the use of cone beam computed tomography in airway imaging: A review. *Semin Orthod.* 2009;15:63-69.

11. Aboudara C.A., Hatcher D, Nielsen I.L. and Miller A., A three-dimensional evaluation of the upper airway in adolescents. *Orthodontics & craniofacial research.* 2003;6 Supp1:173-175.

12. Pham D, Xu C, Prince J. Current methods in medical image segmentation. *annu rev biomed eng.* 2000;02:315-37.

13. Huynh J., Kim D. and McQuilling M., Pharyngeal airflow analysis in obstructive sleep apnea patients pre- and post-maxillomandibular advancement surgery. *J of fluids Eng.* 2009;131:091101-091111.

14. Sharma S. and Sharma P. A, novel technique of skeletonization for feature extraction in cadastral maps. *IJECSE.* 2012;1:1057-1061.

15. http://biomedical.materialise.com/mis.

Chapter 4

Cone-beam computed tomography registration for 3D airway analysis based on anatomical landmarks*

Alsufyani NA, Dietrich NH, Lagravere MO, Carey JP, Major PW
*Published in Oral Surg, Oral Med, Oral Pathol and Oral Radiol *OOOO*. (2014) 118, 371–383.

Preface

This project was a collaboration between the Departments of Mechanical Engineering and Dentistry at the University of Alberta. I was responsible for the data collection and analysis, contributed to concept formation and manuscript composition. From the Mechanical Engineering, N. Dietrich assisted with the data collection and analysis as well as the manuscript composition. Dr. M. Lagravere (from Dentistry) and Prof. J. Carey (from Engineering) were the supervisory authors and were involved with concept formation and manuscript composition. Dr. Paul Major is the supervising author to this thesis and was involved with concept formation and manuscript composition.

This research project, of which this thesis is a part, received research ethics approval from the University of Alberta Research Ethics Board, Project Name "Cone-beam computerized tomography registration for 3D airway analysis based on anatomical landmarks.", Pro00036840, January 29, 2013.

4. Cone-beam computed tomography registration for 3D airway analysis based on anatomical landmarks

Abstract

Objectives: explore craniofacial landmarks reliability to superimpose CBCT images and assess impact of plane re-orientation on airway parameters. **Study design:** 10 CBCTs were marked 3 times at baseline, 3T1, to test landmark reliability. Measurement errors (MEs) of new coordinate system were tested using 3T1, and other 10 paired CBCT images, at *T1* and *T2*. Impact on upper airway was assessed using volume, surface area, and point-based analysis. **Results:** tips of nasal bone and clivus, and foramina spinosa defined the new coordinate system. Plane re-orientation didn't affect landmark identification reliability and significantly reduced inter-landmark distances from T1-T2. Airway volume changed by 25.76±24.9%, surface area by 13.85±10.8%, and mean part analysis was 0.43±0.3 mm. Strong correlation (R >65%) was found between airway analysis and large distances in 2nd and 3rd cervical vertebrae. **Conclusions:** coordinate transformation significantly reduced MEs in longitudinal CBCT data, however is not designed to correct for large neck flexion.

4.1 Introduction

Three-dimensional (3D) models of the upper airway reconstructed from cone-beam computed tomography (CBCT) scans are emerging as methods to assess anatomical constrictions in subjects with symptoms of sleep disordered breathing (SDB) that may also present with craniofacial growth discrepancies.[1] 3D superimposition of CBCT images, before and after treatment, is required to assess anatomically and/or functionally treatment outcomes in this population. The goal is to understand how changes in size and shape of structures are contributed to the surgical treatment. Such understanding can improve our interpretation of variations in patient response and criteria for future treatment planning.[2]

The problem with CBCT superimposition, however, is to determine a method that eliminates or minimizes the impact of variations in patients' head position at different image acquisition times. One technique for CBCT image superimposition is computer-aided superimposition based on best fit of object shapes in the cranial base.[3-6] Another is to standardize and optimize the orientation of two sets of 3D images by transforming the global coordinate system to a new Cartesian coordinate system using reliable anatomical landmarks.[7-9] The latter allows the researcher to quantify the change in a given 3D model in the x, y, z axes i.e. expressing magnitude and direction of change in all three axes.

Several studies reported accuracy and reliability of craniofacial landmarks or their use as reference planes for 3D image superimposition.[4, 6, 8, 10-12] However, these studies were serial 3D cephalometric analysis for "bony" growth assessment, assessing maxillary expansion, or post-orthognathic surgery. A stable reference for a soft tissue structure superimposition, i.e. the upper airway, is required for an adequate registration of longitudinal CBCT images. No soft-tissue structure, including the upper airway, is stable enough to allow registration between pre and post

treatment images, because the shape of the nasopharyngeal airway is affected by changes in head posture, tongue and epiglottis position between both image sets.[5]

To date, the use of craniofacial anatomical landmarks for upper airway (nasal and pharyngeal) registration has not been assessed. The purposes of this study were: 1) to explore reliability of craniofacial landmarks to superimpose upper airway using CBCT images. 2) To assess if plane re-orientation based on these landmarks, affects their reliability, in a single CBCT set. 3) To test the effect of plane re-orientation on airway model superimposition in longitudinal CBCT sets.

4.2 Methods

Reliability of anatomical landmarks

Ten CBCT images of adolescents (age range 13-17) with "normal" upper airways were randomly and retrospectively selected from the Orthodontic Graduate clinic database at the University of Alberta. The images were acquired by the Classic iCAT CBCT scan (Imaging Sciences International, Hatfield, PA). CBCT protocol used a medium-large field of view (16 cm width x 13 cm height), 120 kVp, 24 mAs, 20 seconds scan time, and 0.3 mm voxel size. Patients head is positioned using laser beams within the CBCT scanning machine to maximize position standardization. Using Mimics® software [Mimics 15.0, Materialise NV, Leuven, Belgium], the location of a landmark was marked with 0.5 mm diameter spheres. The software used the center of these spheres as coordinates. A total of 22 landmarks were tested, table 4.1 and Figure 4.1, 14 were in the cranial base (to produce origins for coordinate transformation) and 8 were located at the periphery of the nasal and pharyngeal airway (to test the impact of coordinate transformation on the actual airway).

Table 4.1: Three-dimensional definitions of the anatomical landmarks

Anatomical landmark	Definition	Identification of the landmark on CBCT image section		
		Axial	Coronal	Sagittal
Foramen Cecum **(CECM)** Figure 4.1a	Opening of small foramen at the inferior end of frontal crest of frontal bone.	inferior, complete circle at the frontal-ethmoid bone junction	Superior opening through the roof of ethmoid, anterior to crista galli.	Superior opening through the frontal-ethmoid bone junction, at the inferior end of frontal crest.
Tip of nasal bone **(NSTP)** Figure 4.1a	Tip of two oblong bones joined at the mid-upper face. Their junction forms the nasal bridge.	Mid-inferior radiopaque point of the nasal bone.	Mid-anterior radiopaque point of the nasal bone.	Inferior radiopaque point of the nasal bone.
Anterior nasal spine **(ANS)** Figure 4.1a	Tip of bony projection formed by the union of the two pre-maxillae.	Mid-anterior point	Anterior radiopaque point	Anterior-inferior point
Posterior nasal spine **(PNS)** Figure 4.1a	Tip of the sharp posterior end of the nasal crest of the hard palate.	Mid-posterior point	Mid-inferior point	Posterior-inferior point
Tip of clivus **(CLVS)** Figure 4.1b	Tip of the bony slope posterior to dorsum sallae. It forms the anterior aspect of foramen magnum.	Mid-inferior point of the clivus where right and left basi-occiput join.	Mid-posterior point of the clivus where right and left basi-occiput join.	Inferior point of the clivus.
Foramen magnum **(MGNM)** Figure 4.1b	Mid-posterior point of the large opening in the occipital bone/cranial base.	Mid-anterior point where right and left squama occipitalis join.	Mid-inferior point where right and left squama occipitalis join.	Inferior point of occipital bone.
2nd cervical vertebra **(C2)** Figure 4.1b	Anterior-inferior point of the body of the second cervical spinal vertebra (axis)	Mid-inferior point of the anterior surface of the vertebral body.	Mid-anterior point of the vertebral body	Inferior-anterior corner of the vertebral body.
3rd cervical vertebra **(C3)** Figure 4.1b	Anterior-inferior point of the body of the third cervical spinal vertebra			

Table 4.1 Continued: Three-dimensional definitions of the anatomical landmarks

Anatomical landmark	Definition	Identification of the landmark on CBCT image section		
		Axial	**Coronal**	**Sagittal**
Foramen ovale **(ROVAL, LOVAL)** Figure 4.1c	Mid-foramen in the cranial base/ posterior part of sphenoid bone.	Mid-point of the inferior complete circle representing the foramen.	Mid-point of the medio-lateral and superior-inferior dimensions of the foramen.	Mid-point of the anterior-posterior and superior-inferior dimensions of the foramen.
Foramen spinosum **(RSPNM, LSPNM)** Figure 4.1c	Mid-foramen in the cranial base/ posterior part of sphenoid bone lateral to foramen ovale.	Mid-point of the inferior complete circle representing the foramen.	Inferior, mid-point of the opening to infra-temporal fossa.	
Pterygoid hamulus **(RHMUL, LHMUL)** Figure 4.1d	Tip of hook-like process of the medial pterygoid plate of the sphenoid bone.	Most inferior radiopaque point along the hamular process.		Most lateral radiopaque point of the hamular process.
Infra-orbital foramen **(RORB, LORB)** Figure 4.1e	Mid-foramen in the facial skull below the inferior margin of the orbits.	Mid-point of the widest (medio-lateral) dimension of the foramen	Mid-incomplete circle lateral to the maxillary sinuses. (complete circle represents infra-orbital CANAL)	Mid-point of the superior-inferior dimension of the foramen.
Posterior clinoid process **(RCLIN, LCLIN)** Figure 4.1f	The lateral-superior tubercles of dorsum sellae of the sphenoid bone.	Lateral point of the posterior clinoid process.	Superior-lateral point of posterior clinoid process.	Most lateral radiopaque point posterior to sella turcica.
Greater palatine foramen **(RGPF, LGPF)** Figure 4.1g	Mid of bilateral opening on the posterior angle of the hard palate.	Mid-inferior, most complete circle representing the foramen.	Mid-inferior point of the medio-lateral dimensions of the foramen.	Mid-inferior point of the anterior-posterior dimensions of the foramen.
Spheno-palatine foramen **(RSPPF, LSPPF)** Figure 4.1h	Mid of bilateral openings in the skull connecting nasal cavity with the pterygopalatine fossa.	Mid-point of the medial aspect of the foramen.	Mid-point of the medio-lateral and superior-inferior dimensions of the foramen.	Not reliable

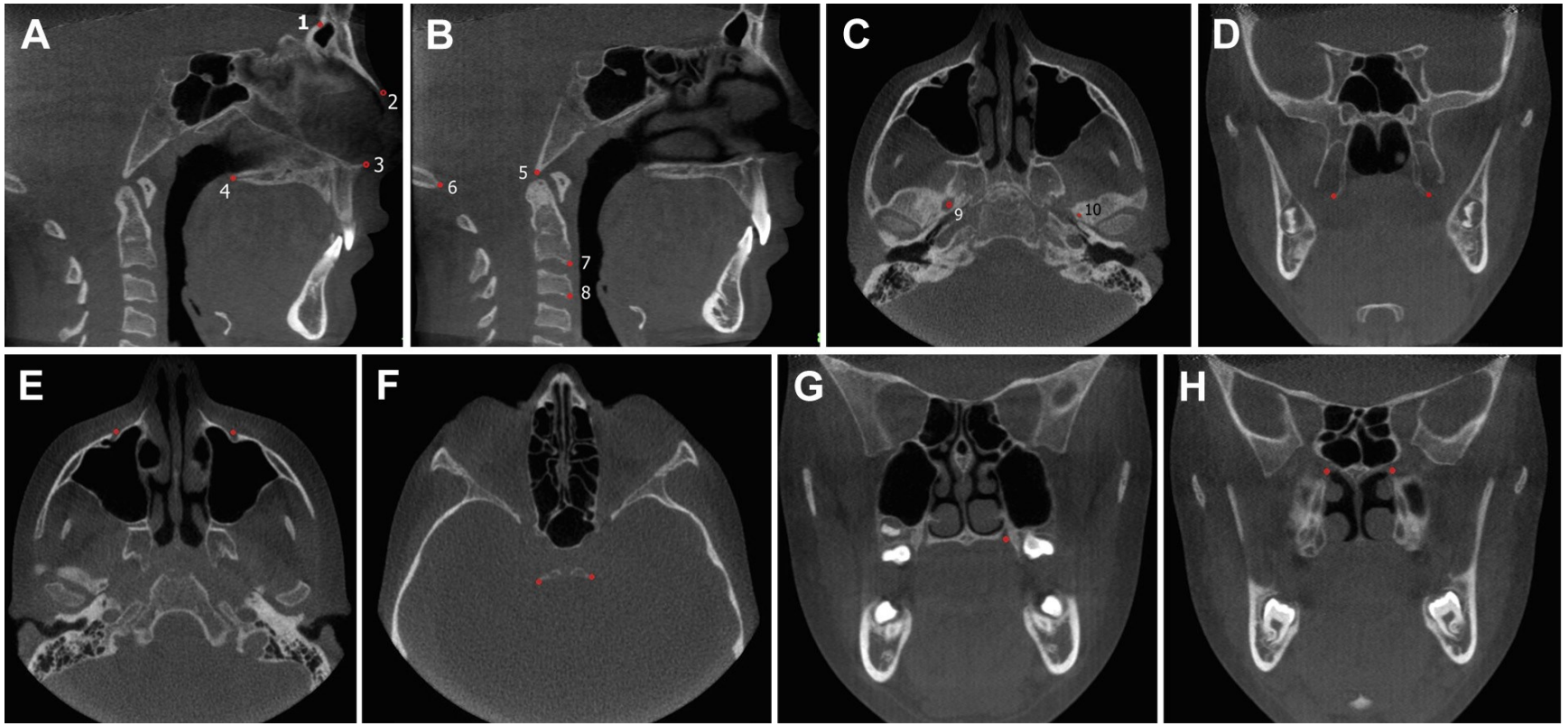


Figure 4.1: CBCT image slices of the registration landmarks. (A) Midsagittal CBCT image showing: 1. Foramen cecum, 2. Tip of nasal bone, 3. Anterior nasal spine, 4. Posterior nasal spine. (B) Midsagittal CBCT image showing: 5. Tip of clivus, 6. Foramen magnum, 7. C2, 8. C3. (C) Axial CBCT image showing: 9. Foramen ovale, 10. Foramen spinosum. (D) Coronal CBCT image showing the tips of the right and left hamular processes. (E) Axial CBCT image showing the right and left infraorbital foramina. (F) Axial CBCT image showing right and left posterior clinoid processes. (G) Coronal CBCT image showing the left greater palatine foramen. (H) Coronal CBCT image showing the right and left sphenopalatine foramina

Two examiners marked the landmarks. The first examiner (#1) marked each landmark three times one week apart. The second examiner (#2), also experienced in CBCT landmark identification and registration, marked the same landmarks one time only. Intra- and inter-examiner agreement were evaluated for examiner #1 and between both examiners, respectively, using intra-class correlation co-efficient (ICC). Also, measurement error (in mm) between each trial for each axis (x, y, z) was calculated for examiner #1, and between examiner #2 and the second trial of examiner #1. A landmark would be considered clinically reliable if it presented > 90% ICC and less than 1.5mm mean difference, in intra- and inter-examiner attempts. Upper airway segmentation and landmark positioning were completed using Mimics® software [Mimics 15.0, Materialise NV, Leuven, Belgium]. Of note, the Cartesian coordinate system provided by Mimics®, transformed and optimized throughout this study is that where x represents the axial plane, y represents the sagittal plane, and z represents the coronal plane. This is unlike the anatomical coordinate system where y is the coronal plane and z is the sagittal plane.

Co-ordinate transformation

Anatomical landmarks tested were ranked based on their ICC and measurement error. The six most reliable landmarks were selected to create the new 3D coordinate system with the highest ranking being the (0, 0, 0) origin point. The second through fourth ranking were used to set the new xy and yz planes. The fifth and sixth ranking points were used to optimize the transformation. The remaining landmarks were used to assess the new coordinate system. Details of the 6-point algorithm for co-ordinate transformation can be reviewed in previous work by Lagravere et al[7] and DeCesare et al[13].

The coordinate transformation was completed in two CBCT data sets:

1) To determine if the coordinate transformation potentially affects the reliability of landmark identification, transformations were applied on the 10 CBCT images at baseline, T1, marked three times by examiner #1 (hereafter, image set referred to as 3T1).
2) To determine if the coordinate transformation potentially produces clinically relevant superimposition error in time, transformations were applied on 10 paired CBCT images, at baseline *T1* and six-months after *T2*, marked one time (hereafter, image set referred to as T1-T2). The 10 paired CBCT images were randomly and retrospectively selected from the Orthodontic Graduate clinic database for subjects that participated in a previous maxillary expansion clinical trial, unrelated to this study.

Once transformations were completed, inter-landmark distance, i.e. measurement error, in the 3T1 and T1-T2 data sets was compared between original and transformed data in all axes. Mean inter-landmark measurement error after transformation less than 1.5 mm was considered clinically acceptable.

Impact of transformation on upper airway

To relate the impact of coordinate transformation on airway parameters, 3D airway models were segmented for all 10 paired CBCT data at T1-T2 (total 20 airway models). Then, each paired CBCT data set was registered, based on the landmarks defining the new coordinate system. The pharyngeal airway (bounded by the inferior-anterior point of the anterior arch of C1 superiorly, to the inferior-anterior point of C3 inferiorly) was semi-automatically segmentation using grey-level thresholding (ranged from -1000 to -600) in *Mask tool* in Mimics® software

[Mimics 15.0, Materialise NV, Leuven, Belgium]. Image sets were registered using *Image registration tool* in Mimics®. The 3D airway models were then exported to 3-matic® [3-matic 7.0, Materialise NV, Leuven, Belgium] in ASCII STL format where total volume and total surface area were measured for each airway model. In addition, a point-based analysis using the *Part comparison analysis* tool in 3-matic® was used. This tool allows quantified comparison of the airway model at T2 (target entity) to the airway model at T1 (reference entity).

Thousands of triangles form the mesh model of an upper airway. Part comparison analysis measures the distance (in mm) between sampled or patch-based triangular nodes from one object (the target) to the closest triangular node on the surface of the "reference" object. This type of analysis is useful to compare two, very similar geometries to evaluate the accuracy of one of the two, or to study the effect of a certain parameter over time. The analysis calculates the mean, minimum, and maximum values of these distances then produces a color map, Figure 4.2. The mean is a weighted mean that takes the triangle size into account. The operator is allowed to change the upper and lower thresholds, of the distances, such that all triangles are colored:

- Blue [minimum part analysis]: if the triangular node travelled a distance below the minimum threshold value (values are negative).
- Red [maximum part analysis]: if the triangular node travelled a distance above the maximum threshold value (values are positive).
- Green: if the triangular node travelled a distance within the threshold boundaries.

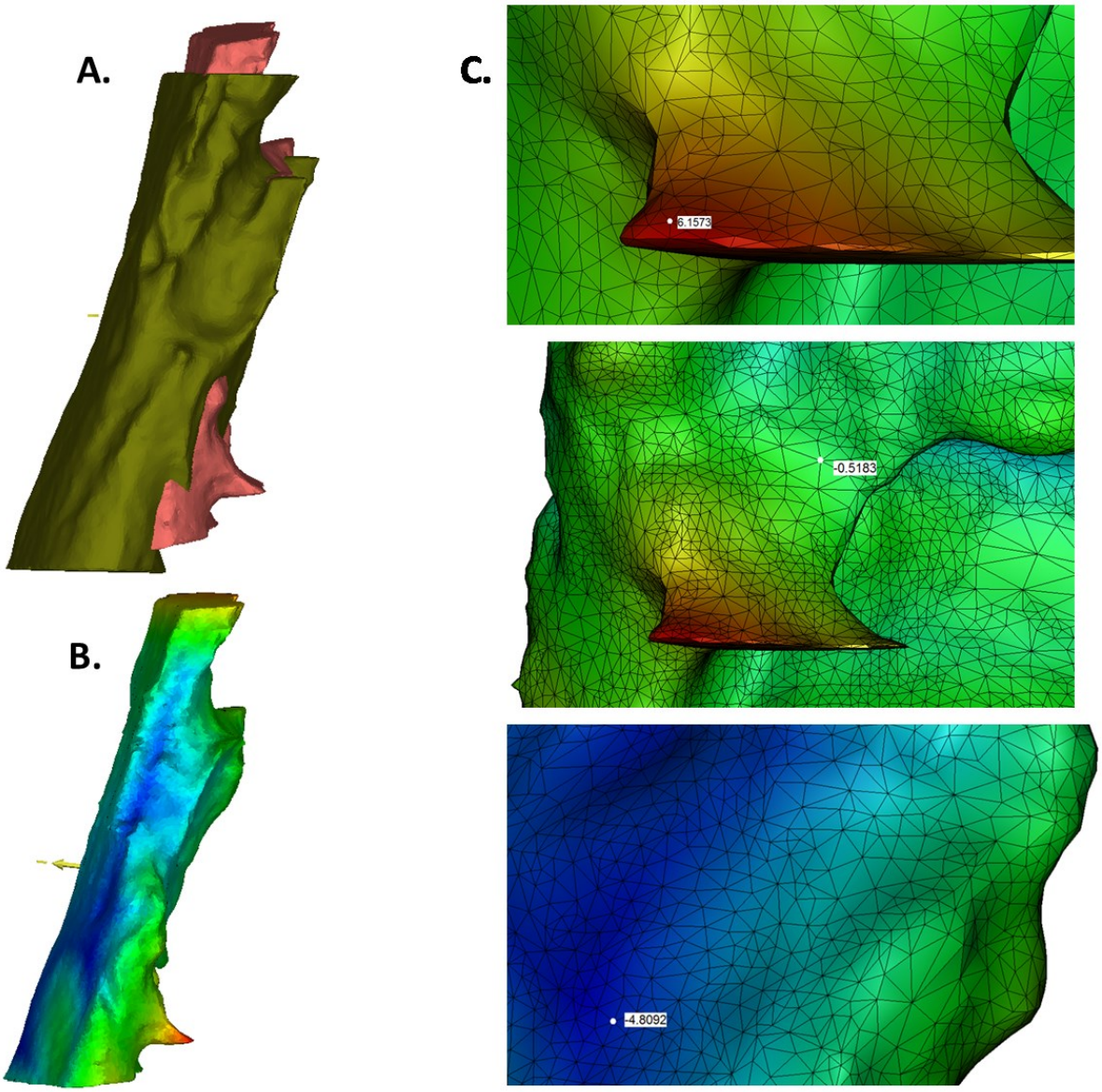


Figure 4.2: Part Comparison analysis of the oropharyngeal airways (A) Superimposed 3D airway models at T1 (pink) and T2 (olive-green). (B) Part Comparison applied on T1. (C) Magnified areas into the mesh showing, from top to bottom, maximum part analysis: red triangle with distance of 6.1573 mm, part analysis within the threshold: green triangle with distance of -0.5183 mm, and minimum part analysis: blue triangle with distance of -4.8092 mm.

Due to the lack of sufficient literature reporting the changes in airway measurements at which clinical significance is noted, the threshold for Part comparison analysis was conservatively set at 2 mm. The mean, minimum, and maximum part analysis were measured between each airway pair (from T2 airway model to the surfaces of T1 airway model).

Statistical analyses (ICC, means and standard deviations of measurement errors, and correlations) were assessed using IBM SPSS® [IBM SPSS Statistics, V 21.0, Armonk, NY].

4.3 Results

Reliability of anatomical landmarks

Intra-examiner reliability was high; overall ICC was >98% and the lowest ICC lower bound was 95% for RHMU and RCLIN in the y-axis. The intra-examiner mean measurement error (ME) was overall low; up to 0.50 mm. The maximum ME was <1.5 mm except for RCLIN in y and z-axes (= 1.60 mm).

Inter-examiner reliability was high; overall ICC was >95% except for 88 % for LORB in the y-axis. Overall, the mean inter-examiner ME was <1.5 mm. Maximum ME > 1.5 mm was found in CECM (1.99mm-z axis), RHMU (2.2mm-y axis), RORB (2.79mm-y axis), LORB (2mm-x axis/2.7 mm-y axis), and LCLIN (2.18mm-y axis). Average ME for all landmarks are listed in table 4.2.

Table 4.2: Average mean of measurement error in 3T1 (original) data

Landmarks*		Mean ±standard deviation (mm)					
		Intra-examiner			Inter-examiner		
		x	y	z	x	y	z
1	CECM	0.15±0.2	0.36±0.23	0.52±0.40	0.25±0.24	0.40±0.30	0.71±0.59
2	NSTP	0.45±0.25	0.31±0.14	0.37±0.25	0.56±0.37	0.60±0.27	0.31±0.21
3	CLVS	0.27±0.11	0.54±0.15	0.45±0.30	0.54±0.35	0.30±0.25	0.40±0.25
4	MGNM	0.22±0.18	0.26±0.17	0.37±0.34	0.34±0.17	0.24±0.17	0.45±0.24
5	ROVAL	0.26±0.26	0.29±0.26	0.10±0.17	0.27±0.36	0.57±0.57	0.87±0.44
6	LOVAL	0.26±0.16	0.26±0.21	0.13±0.19	0.28±0.17	0.65±0.41	0.36±0.25
7	RSPNM	0.27±0.18	0.38±0.20	0.45±0.55	0.38±0.29	0.47±0.15	0.69±0.47
8	LSPNM	0.38±0.27	0.32±0.19	0.23±0.21	0.17±0.15	0.52±0.37	0.54±0.39
9	RHMU	0.46±0.35	0.60±0.41	0.28±0.27	0.53±0.34	1.52±0.73	0.66±0.50
10	LHMU	0.32±0.31	0.61±0.29	0.33±0.17	0.54±0.25	1.05±0.49	0.51±0.36
11	RORB	0.33±0.18	0.51±0.22	0.27±0.22	0.61±0.39	1.71±0.57	0.55±0.33
12	LORB	0.46±0.16	0.42±0.19	0.37±0.22	0.74±0.57	1.93±0.61	0.72±0.59
13	RCLIN	0.06±0.09	0.55±0.43	0.55±0.45	0.34±0.27	0.52±0.36	0.33±0.30
14	LCLIN	0.10±0.10	0.52±0.61	0.52±0.27	0.28±0.18	0.74±0.73	0.40±0.26
15	ANS	0.37±0.16	0.27±0.28	0.42±0.19	-		
16	PNS	0.23±0.08	0.20±0.24	0.30±0.24			
17	C2	0.36±0.20	0.50±0.22	0.36±0.37			
18	C3	0.33±0.12	0.33±0.26	0.26±0.22			
19	RGPF	0.27±0.12	0.33±0.11	0.46±0.22			
20	LGPF	0.10±0.10	0.17±0.09	0.20±0.15			
21	RSPPF	0.15±0.07	0.13±0.11	0.23±0.19			
22	LSPPF	0.42±0.18	0.21±0.20	0.40±0.34			

Abbreviations: CECM: Foramen cecum, NSTP: Tip of Nasal bone, CLVS: Tip of clivus, MGNM: Dorsum foramen Magnum, ROVAL/LOVAL: Foramen ovale (R, L), RSPNM/LSPNM: Foramen Spinosum (R, L), RHMU/LHMU: Tip of hamulus (R, L), RORB/LORB: Infra-orbital foramen (R, L), RCLIN/LCLIN: Posterior clinoid processes (R, L), ANS: Anterior nasal spine, PNS: Posterior nasal spine, C2: Anterior-inferior point C2, C3:Anterior-inferior point C3, RGPF/LGPF: Greater palatine foramen (R,L), RSPPF/LSPPF: Sphenopalatine foramen (R,L)

*Landmarks 15 through 22 were specifically chosen at the proximity of the upper airway to test effects of transformation on airway, hence inter-examiner reliability and measurement error was not attained.

To proceed with the coordinate transformation, four landmarks were excluded from the total 22. These were: CECM and MGNM (as they were located at the periphery of the image volume), RORB and LORB due to their high mean ME.

Co-ordinate transformation

The landmarks chosen to form the coordinate system were: NSTP, CLVS, RSPNM, LSPNM, ROVAL and LOVAL. NSTP was chosen as the (0, 0, 0) origin point. The new xy-plane was defined using RSPNM and LSPNM with NSTP. The new yz-plane was formed by NSTP and CLVS perpendicular to the new xy-plane, Figure 4.3. ROVAL and LOVAL were used to optimize the transformation 6-point.

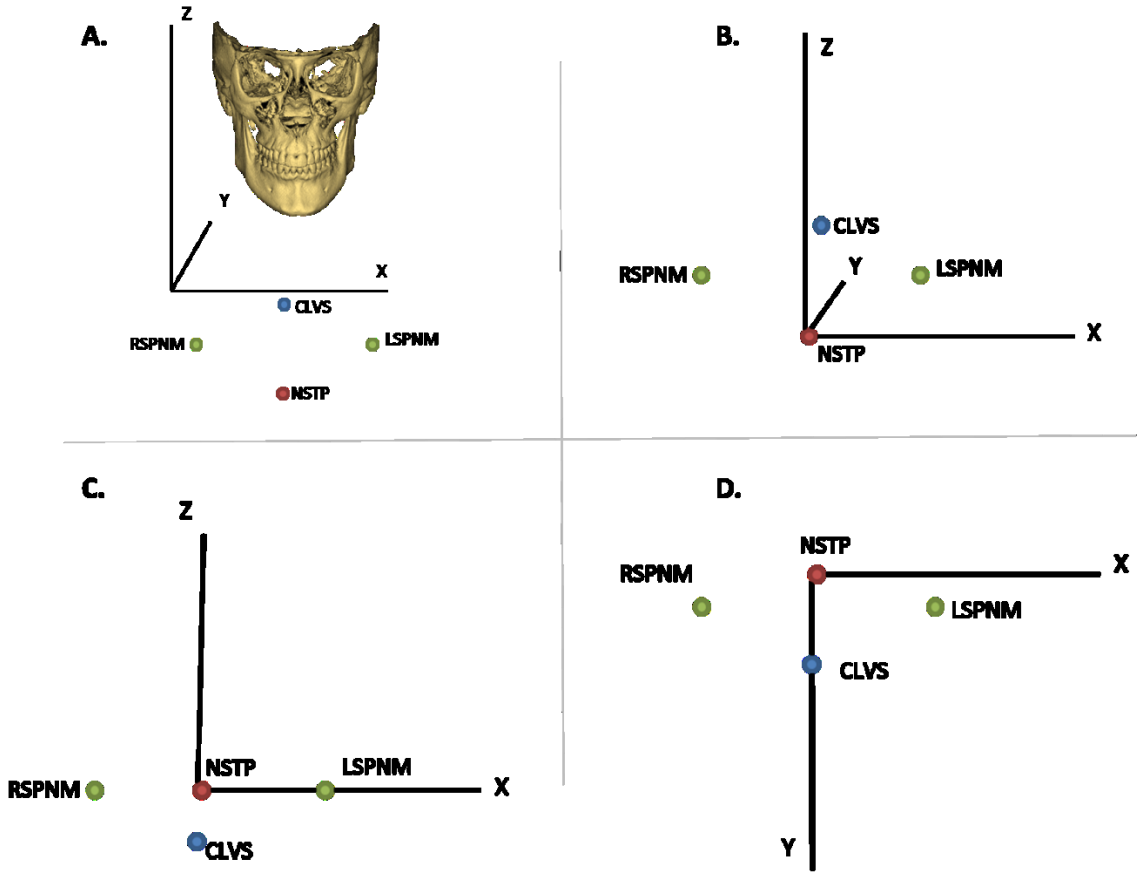


Figure 4.3: Co-ordinate system transformation sequence. (A) Location of four landmarks in global co-ordinate system. (B) Translation of the center of global co-ordinate system to NSTP. (C) Determination of new xy-plane using NSTP, RSPNM and LSPNM. (D) Determination of new yz-plane using NSTP and CLVS. *NSTP: Tip of Nasal bone, CLVS: Tip of clivus, RSPNM/LSPNM: Foramen Spinosum (right, left).*

MEs of inter-landmark distance in 3T1 data after coordinate transformation, with comparison to the original data with T1-T2 data are summarized in tables 4.3 and 4.4, respectively. In 3T1 data, the average ME after coordinate transformation was less than 1.5 mm for all landmarks. In comparison to the original MEs, the transformation either reduced or increased (noted by – in the mean differences when the transformed values are subtracted from the original) the original average ME by <0.5 mm except for C3 which showed an increased average ME of 1.03 ±0.31 mm in the x-axis, table 4.3.

Table 4.3: Average mean of measurement error in 3T1 data after transformation

Landmarks*	After transformation Mean ±SE (mm)			Difference in ME= original – transformed Mean ±SE (mm) (95% Confidence Interval)		
	x	y	z	x	y	z
NSTP	0±0	0±0	0±0	NA	NA	NA
CLVS	0 ±0	0.38 ±0.26	0.47±0.40	NA	0.16±0.08 (-0.02, 0.36)	-0.01±0.15 (-0.37, 0.34)
ROVAL	0.37±0.16	0.43±0.26	0.87±0.21	-0.12±0.08 (-0.32, 0.76)	-0.14±0.07 (-0.32, 0.03)	-0.76±0.07† (-0.94, 0.51)
LOVAL	0.28±0.14	0.45±0.34	0.74±0.36	-0.02±0.06 (-0.16, 0.11)	-0.20±0.07† (-0.36,0.03)	-0.61±0.07† (-0.78, -0.43)
RSPNM	0.32±0.16	0.31±0.20	0±0	-0.05±0.05 (-0.19, 0.07)	0.06±0.06 (-0.07, 0.20)	NA
LSPNM	0.42±0.15	0.42±0.25	0±0	-0.04±0.07 (-0.21, 0.13)	-0.09±0.05 (-0.21, 0.01)	NA
RHMU	0.90±0.43	0.52±0.29	0.60±0.24	-0.44±0.12† (-0.73, -0.16)	0.07±0.05 -0.04, 0.20	-0.32±0.10† (-0.56, -0.07)
LHMU	0.86±0.29	0.57±0.26	0.66±0.40	-0.54±0.08† (-0.74, -0.34)	0.04±0.06 (-0.09, 0.17)	-0.33±0.09† (-0.55, -0.11)
RCLIN	0.71±0.43	0.48±0.26	0.81±0.28	-0.65±0.13† (-0.96, -0.33)	0.07±0.08 (-0.11, 0.26)	-0.26±0.16 (-0.64, 0.10)
LCLIN	0.67±0.40	0.41±0.26	0.73±0.32	-0.57±0.13† (-0.87,-0.27)	0.11±0.21 (-0.37, 0.58)	-0.21±0.08† (-0.40, -0.01)
ANS	1.14±0.33	0.46±0.24	0.63±0.24	-0.76±0.10† (-0.99, -0.53)	-0.19±0.08 (-0.38,0.004	-0.21±0.07† (-0.38, -0.04)
PNS	0.52±0.36	0.34±0.27	0.60±0.24	-0.29±0.11† (-0.54,-0.03)	-0.14±0.07 (-0.31, 0.01)	-0.30±0.06† (-0.45, -0.16)
C2	1.11±0.64	0.70±0.33	0.65±0.40	-0.75 ±0.20† (-1.21, -0.29)	-0.20±0.08† (-0.4, -0.01)	-0.28±0.11† (-0.55, -0.01)
C3	1.37±0.94	0.63±0.37	0.71±0.42	-1.03 ±0.31† (-1.7, -0.31)	-0.3±0.07† (-0.48, -0.13)	-0.45±0.09† (-0.66, -0.23)
RGPF	0.76±0.31	0.43±0.20	0.67±0.44	-0.50±0.11† (-0.76, -0.23)	-0.10±0.06 (-0.25, 0.05)	-0.20±0.11 (-0.45, 0.04)
LGPF	0.10±0.10	0.17±0.09	0.20±0.15	-0.58±0.10† (-0.82, -0.33)	-0.14±0.07 (-0.31, 0.02)	-0.32±0.12† (-0.61, -0.02)
RSPPF	0.32±0.12	0.27±0.18	0.52±0.11	-0.16±0.03† (-0.25, -0.08)	-0.14±0.05† (-0.27, -0.01)	-0.29±0.07† (-0.45, -0.12)
LSPPF	0.53±0.11	0.43±0.28	0.63±0.44	-0.11±0.05 (-0.24, 0.02)	-0.21±0.03† (-0.29, -0.14)	-0.23±0.11 (-0.48, 0.02)

Abbreviations: CECM: Foramen cecum, NSTP: Tip of Nasal bone, CLVS: Tip of clivus, MGNM: Dorsum foramen Magnum, ROVAL/LOVAL: Foramen ovale (R, L), RSPNM/LSPNM: Foramen Spinosum (R, L), RHMU/LHMU: Tip of hamulus (R, L), RORB/LORB: Infra-orbital foramen (R, L), RCLIN/LCLIN: Posterior clinoid processes (R, L), ANS: Anterior nasal spine, PNS: Posterior nasal spine, C2: Anterior-inferior point C2, C3:Anterior-inferior point C3, RGPF/LGPF: Greater palatine foramen (R,L), RSPPF/LSPPF: Sphenopalatine foramen (R,L)

†P< 0.05 based on One way ANOVA.

In T1-T2 data, the original average MEs were very high, up to 7.26 mm. After coordinate transformation, the average MEs were less than 1.5 mm for all landmarks except C2 (1.78±0.94 mm in y-axis) and C3 (2.96±1.47 mm in y-axis). In comparison to the original MEs, the transformation significantly reduced the inter-landmark distance especially in the y and z-axes, table 4.4.

Table 4.4: Average measurement error between T1-T2 (original and transformed)

Landmarks	T1-T2 M±SD (mm)						Difference Original vs. transformed M±SE (mm) (95% Confidence Interval)		
	Original data			Transformed data					
	x	**y**	**z**	**x**	**y**	**z**	x	y	z
NSTP	1.64±2.37	5.39±4.42	4.77±2.81	NA			NA		
CLVS	2.30 ±1.69	6.29 ±5.91	5.55±5.13	NA	0.08±0.19	0.19±0.32	NA	6.21±1.89* (1.92,10.50)	5.36±1.65* (1.61, 9.10)
ROVAL	1.60±1.46	6.31±4.91	4.37±4.31	0.29±0.35	0.68±0.84	0.52±0.60	1.30±0.49* (0.17, 2.43)	5.6±1.60† (2.00, 9.25)	3.85±1.43* (0.60, 7.10)
LOVAL	1.59±1.47	5.74±4.83	4.52±4.36	0.19±0.13	0.79±0.67	0.47±0.37	1.39±0.48* (0.31, 2.48)	4.94±1.60* (1.31, 8.57)	4.05±1.37* (0.95, 7.15)
RSPNM	1.91±1.64	6.14±4.83	4.43±4.66	0.02±0.05	0.14±0.38	NA	1.89±0.51† (0.73, 3.06)	6.00±1.54† (2.50, 9.50)	NA
LSPNM	1.93±1.78	5.97±5.06	4.35±4.48	0.03±0.06	0.13±0.39	NA	1.90±0.55† (0.64, 3.16)	5.84±1.64† (2.12, 9.55)	NA
RHMU	2.08±2.23	6.80±6.35	3.95±4.04	0.65±0.45	0.71±0.71	0.33±0.33	1.42±0.77 (-0.32, 3.18)	6.09±2.09* (1.34, 10.83)	3.61±1.31* (0.63, 6.60)
LHMU	2.29±2.03	6.36±6.30	3.60±3.83	0.77±0.57	1.01±0.80	1.00±0.73	1.51±0.72 (-0.11, 3.14)	5.26±2.01* (0.71, 9.81)	2.60±1.16 (-0.03, 5.23)
RCLIN	1.31±1.39	5.41±4.63	4.76±4.61	0.34±0.22	0.67±0.70	0.53±0.39	0.97±0.43 (-0.01, 1.96)	4.74±1.58* (1.16, 8.33)	4.22±1.51* (0.80, 7.65)
LCLIN	1.31±1.29	6.09±4.80	4.47±4.82	0.27±0.18	1.16±1.08	0.75±0.76	1.04±0.40* (0.11, 1.96)	4.92±1.46† (1.60, 8.23)	3.71±1.64* (-0.01, 7.44)
ANS	1.96±2.50	6.26±5.90	4.30±2.92	0.38±0.20	0.49±0.57	0.47±0.39	1.57±0.82 (-0.29, 3.45)	5.77±1.91* (1.44, 10,11)	3.83±0.98† (1.61, 6.05)
PNS	1.73±2.19	6.40±5.97	3.50±4.30	0.40±0.28	0.77±0.69	0.45±0.39	1.32±0.65 (-0.16, 2.81)	5.62±1.94* (1.21, 10.03)	3.06±1.40 (-0.12, 6.24)
C2	2.74±2.49	7.26±7.06	5.41±4.89	0.79±0.71	1.78±0.94	0.84±1.05	1.95±0.87 (-0.02, 3.92)	5.47±2.21* (0.45, 10.50)	4.56±1.57* (1.00, 8.13)
C3	2.90±2.76	7.15±7.66	5.96±5.03	1.05 ±0.74	2.96±1.47	1.23±1.46	1.85±0.96 (-0.33, 4.04)	4.18±2.48 (-1.44, 9.81)	4.73±1.77* (0.71, 8.74)

Table 4.4 Continued: Average measurement error between T1-T2 (original and transformed)

Landmarks	T1-T2 M±SD (mm)						Difference Original vs. transformed M±SE (mm) (95% Confidence Interval)		
	Original data			Transformed data					
	x	y	z	x	y	z	x	y	z
RGPF	1.62±2.30	6.46±6.18	3.38±3.77	0.70±0.34	0.60±0.57	0.64±0.70	0.92±0.77 (-0.82, 2.66)	5.85±1.99* (1.34, 10.36)	2.73±1.30 (-0.19, 5.67)
LGPF	1.93±1.92	6.20±5.67	3.25±4.09	0.36±0.40	0.73±0.55	0.69±0.69	1.56±0.65* (0.07, 3.05)	5.46±1.84* (1.28, 9.64)	2.56±1.33 (-0.46, 5.60)
RSPPF	1.32±1.71	6.42±4.88	3.47±4.06	0.60±0.37	0.89±0.83	0.87±0.45	0.73±0.58 (-0.58, 2.04)	5.53±1.52† (2.09, 8.98)	2.60±1.30 (-0.35, 5.55)
LSPPF	1.40±1.58	5.71±4.43	3.65±4.32	0.73±0.36	0.80±0.86	0.47±0.48	0.67±0.43 (-0.30, 1.66)	4.91±1.52* (1.47, 8.36)	3.17±1.37 (0.06, 6.30)

Abbreviations: CECM: Foramen cecum, NSTP: Tip of Nasal bone, CLVS: Tip of clivus, MGNM: Dorsum foramen Magnum, ROVAL/LOVAL: Foramen ovale (R, L), RSPNM/LSPNM: Foramen Spinosum (R, L), RHMU/LHMU: Tip of hamulus (R, L), RORB/LORB: Infra-orbital foramen (R, L), RCLIN/LCLIN: Posterior clinoid processes (R, L), ANS: Anterior nasal spine, PNS: Posterior nasal spine, C2: Anterior-inferior point C2, C3:Anterior-inferior point C3, RGPF/LGPF: Greater palatine foramen (R,L), RSPPF/LSPPF: Sphenopalatine foramen (R,L)
NA: not applicable
†P-value <0.01 *P-Value <0.05; One way ANOVA.

Impact of transformation on upper airway

After registration of T2 to T1 CBCT data sets based on the new coordinate system, the total volume of the upper airway (T1-T2) changed by 25.76±24.9% (2.09±1.95 cm^3) and the total surface area by 13.85±10.8% (4.58±3.95 cm^2). The mean part analysis was 0.43±0.3 mm; the maximum part analysis (over 2 mm in positive direction; marked red in the color map) was 4.39±1.06 mm, and the minimum part analysis (over 2 mm in negative direction; marked in blue in the color map) was 3.82±0.82 mm, table 4.5.

Table 4.5: Changes in airway parameters from T1-T2 after coordinate transformation and registration

Parameters measured		**Mean±SD**	**Minimum**	**Maximum**	**P value**
Volume difference	(cm3)	2.09±1.95	0.34	6.74	NS*
	(%)	25.76±24.95	7.09	87.85	NS*
Surface area difference	(cm2)	4.58±3.95	1.47	13.71	NS*
	(%)	13.85±10.80	4.49	36.78	NS*
Mean part analysis (mm)		0.43±0.3	0.04	0.89	-
Minimum part analysis (mm)		-3.82±0.82	-5.06	-2.06	-
Maximum part analysis (mm)		4.39±1.06	2.44	5.89	-
*NS: not significant using Paired samples T-test					

Larger volume and surface area changes were noted in subjects 8 and 9, Figure 4.4a. The majority of the triangular nodes (forming an airway model; ~2000-5000 triangles) moved <2 mm in both directions. Larger triangular node distances (over 2 mm) were noted in subjects 1, 5, 7, 8, 9, and 10, Figures 4.4b and 4.5)

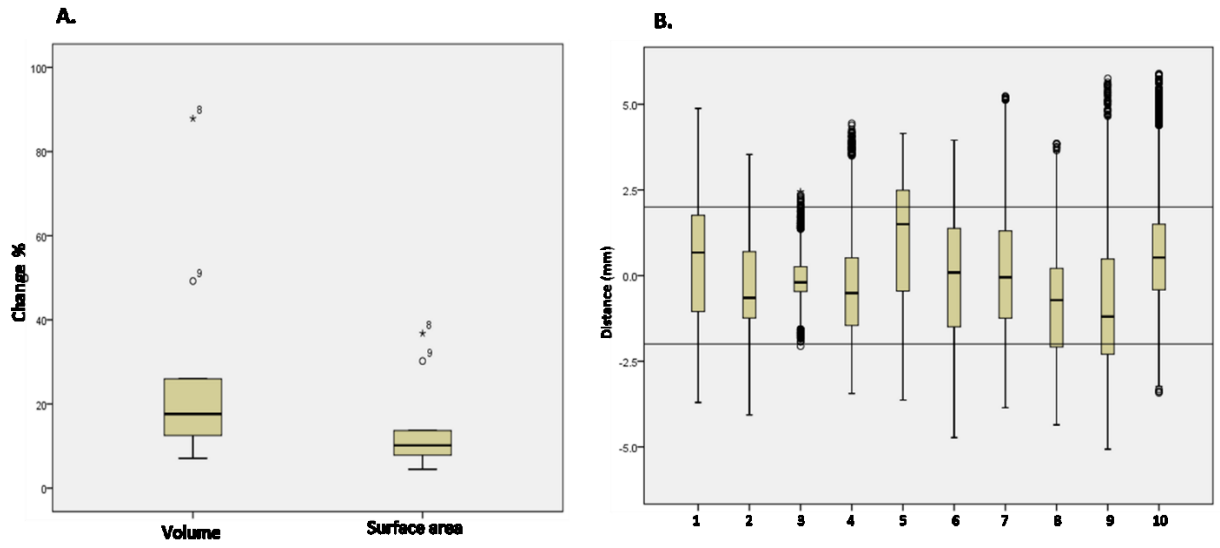


Figure 4.4: Changes in airway from T1 to T2. (A) Scatter plot of the volume and surface area change (%). (B) Scatter plot of the part analysis showing distances travelled by triangular nodes forming the airway, for subject 1 through 10.

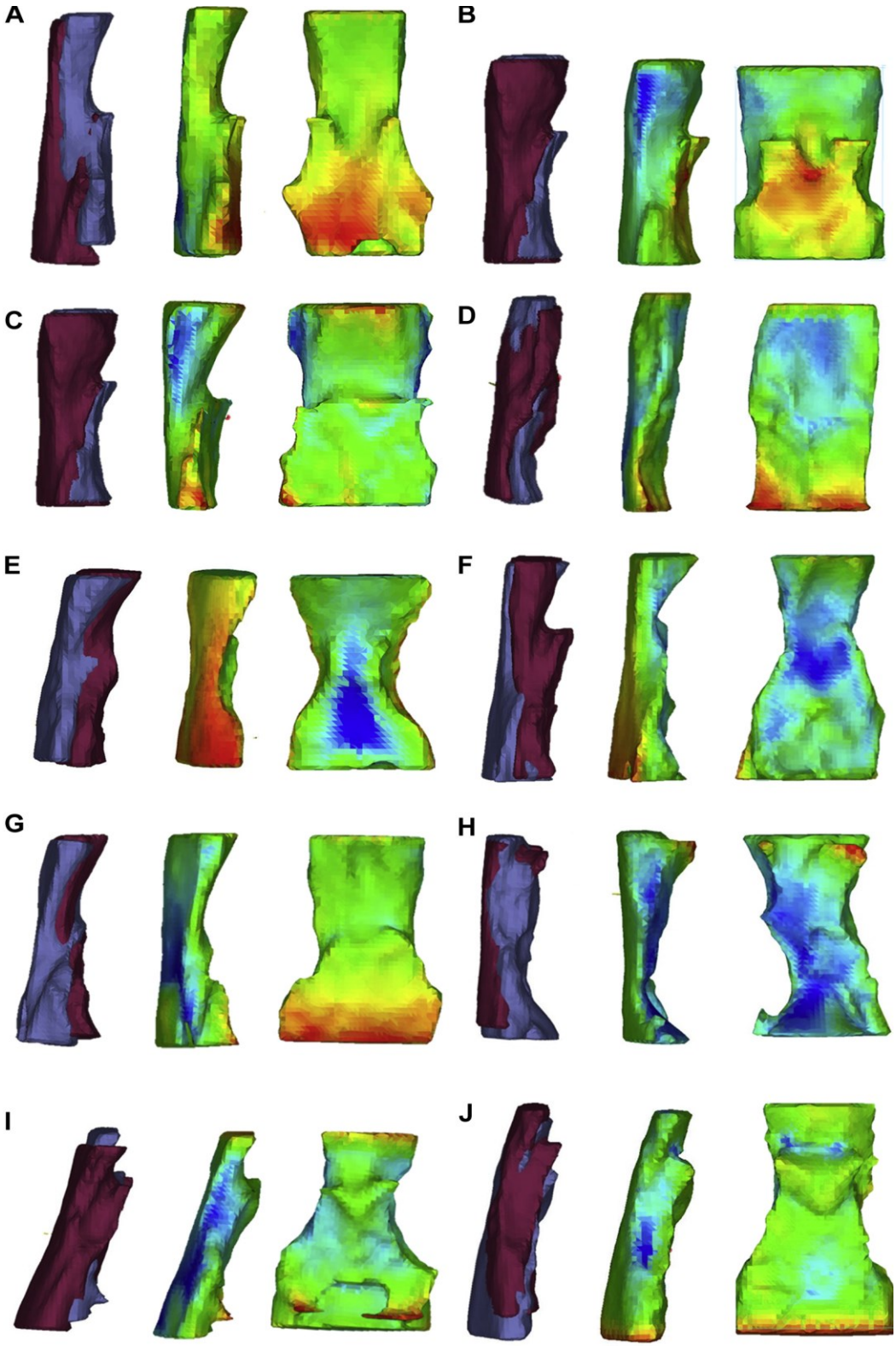


Figure 4.5: Registered 3D models of the 10 pharyngeal airways. A through J correspond to subjects 1 through 10. The purple and blue models represent T1 and T2 airways after registration based on new coordinate transformation; side view. The color-mapped models represent the part analysis; front and side views.

As large inter-landmark distances (>2 mm) were noted in C2 and C3 in several T1-T2 subjects, correlations between C2-C3 inter-distances and changes in 3D airway parameters were assessed. Significant and strong positive correlation was found between the minimum/maximum part analysis distances and changes in C2 and C3 in at least one axis, table 4.6.

Table 4.6: Correlations between C2-C3 inter-distances and changes in 3D airway parameters

Airway parameters	**C2x**	**C2y**	**C2z**	**C3x**	**C3y**	**C3z**
Volume difference (%)	-0.52	-0.16	0.02	-0.01	-0.25	-0.11
Surface difference (%)	-0.51	0.01	0.00	-0.14	-0.32	-0.21
Mean part analysis	-0.29	0.17	0.45	0.08	-0.31	0.31
Minimum part analysis	0.75*	-0.19	0.03	0.65*	0.09	0.16
Maximum part analysis	-0.42	0.74*	0.61	-0.20	0.61	0.38
*Correlation is significant at the 0.05 level (2-tailed).						

4.4 Discussion

Reliability of anatomical landmarks

Although it is impossible to locate a landmark without errors, all efforts should be made to minimize such errors.[14] Landmark identification errors are related mainly to the quality of the images, nature of the landmark (point vs. surface), operator error (reliability), and the registration procedure.[10]

There is insufficient literature reporting the change in linear, area, or volume airway measurements at which clinical significance or impact is noted.[1] Therefore, the 1.5 mm cut-off for mean ME for landmark identification was chosen.[10, 15] Cranial base landmarks can be

identified from CBCT with very good reliability as they are considered anatomically stable structures and by age 5, 85% of growth is completed in this area.[8, 15]

Overall, intra- and inter-examiner reliability were high (ICC >95%). Intra- and inter-examiner mean MEs were generally low (< 1.5 mm). Errors > 1.5 mm were more found between examiners in: CECM, RHMU, RORB, LORB, and LCLIN, table 4.2. Our results presented are in agreement with other studies[10, 16] with reported MEs of 0.1-4 mm or < 1.4 mm. Generally, intra-examiner landmark identification errors are less than inter-examiner errors.[10]

Although mean MEs were <1.5 mm, maximum MEs found in RHMU and LCLIN may be related to examiner differences in location or the impact of image quality on their interpretation. In addition, RORB and LORB presented intra- and inter-examiner difficulties due to the oblique nature of the infra-orbital foramen and the wide range of locating its center especially in the y and z axes. CECM is a very small foramen in the anterior cranial base and maybe absent in some subjects. Although mean ME was <1.5 mm for CECM, maximum ME was found in one axis between both examiners possibly related to the nature of the landmark i.e. small size.

Four landmarks were excluded from further analysis: CECM and MGNM were located at the periphery of the image volume thus risking their non-inclusion in future CBCT scans. Due to their high intra- and inter-examiner mean ME, RORB and LORB were also excluded.

Co-ordinate transformation

Unlike previous studies[3-6] utilizing gray scales and color-coded graphics to display surface changes, the authors here chose coordinate transformation and optimization analysis to superimpose CBCT images. This allows quantified assessment of change in the x, y, and z axes

and involves minimizing the total root mean square error found over a series of fixed landmark positions.

An anatomical coordinate system has higher reproducibility when the distance between those landmarks is great. Objective landmarks, testing the transformation error, should be further away from the landmarks defining the new coordinate system.[17] The landmarks chosen to form the coordinate system were: NSTP, CLVS, RSPNM, LSPNM, ROVAL and LOVAL. The first four were used to define the new coordinate system, ROVAL and LOVAL were used to optimize the location of the defining landmarks yielding a 6-point transformation. The method error in the 6-point transformation algorithm, as presented by DeCesare et al[13], reduced the overall average distance errors from 1.64 ±0.62 mm in the original image to 1.24±0.37 mm in the transformed image.

Because most landmarks presented with excellent intra-reliability and small average measurement errors (0.10–0.61 mm) in all axes, transformation was allowed a maximum of 1 mm shift in landmarks forming the new reference system. Since all landmarks tested in this study may have minor, but not significant, position changes as a result of growth within our 6-month imaging time frame, a maximum ME > 2 mm after transformation was not acceptable.

Changes in inter-landmark distances, MEs, in 3T1 data reflects the sole effects of coordinate transformation i.e. no effect of patient positioning error. The average ME after transformation was less than 1.5 mm for all landmarks. Based on table 4.3, the transformation improved (reduced) the original average ME in some landmarks at the expense of increasing it for others. However, these ME increases were by <0.5 mm except for C3 (increased by 1.03 mm in x-axis). C3 is the furthest landmark from the coordinate-defining landmarks and larger differences at C3 were expected to occur. This is similar to the work by Lagravere et al[8] where

larger errors were found in the R/L mental foramen (~5 mm) when using R/L foramen spinosum and R/L external auditory meatuses for their coordinate system.

In T1-T2 data, we introduce another factor in ME, i.e. alteration in patient position at two different CBCT scans. The mean inter-landmark distances were high in the "original" T1-T2 data, up to 7.26 mm and larger differences were found in the y and z-axes, (table 4.4). This can be explained by the fact that patient positioning in the x-axis (right-left plane) is fairly reproducible using positioning laser-beams within the CBCT machine. Patient positioning in the y-axis (antero-posterior plane) or z-axis (superior-inferior plane) is largely influenced by head rotation and flexion of the neck. If we consider non-absolute values for MEs, patient positioning at T2 compared to T1 caused most of the landmarks to shift to the patients' anterior and inferior (i.e. ME is negative in y and z axes), and slightly to the patients' left (i.e. positive in x-axis).

After T1-T2 co-ordinate transformation, the mean inter-landmark distances were less than 1.5 mm for all landmarks except C2 (1.78 mm) and C3 (2.96 mm). In comparison to the original MEs, the transformation corrected for patient positioning by significantly reducing the inter-landmark distance, especially in the y and z-axes (antero-posterior and superior-inferior direction), table 4.4.

C2 and C3 were chosen specifically to indirectly assess the impact of transformation on the oro-pharyngeal airway. Although coordinate transformation corrected for patient positioning and head rotation from T1-T2, it is not capable of re-aligning deformable anatomy such as that caused by neck flexion in the areas of C2 and C3 (mean MEs > 1.5 mm, maximum MEs up to 4.91 mm). Because the pharyngeal walls are soft tissues formed mainly by muscles and adipose tissue, it is expected to deform in shape due to the displacement pressures from cervical

vertebrae as the neck flexes. It was necessary, therefore, to directly assess the ME within the oropharyngeal airway.

Impact of transformation on upper airway

Neck flexion at T1 or T2 scan, in several subjects, caused maximum MEs of 3.09 mm in y axis and 3.75 mm in the z-axis in C2, and 4.66 mm in the y-axis and 4.91 mm in the z-axis in C3. Consequently, this caused apparent discrepancies between T1-T2 pharyngeal airways, Figure 4.6. This has important consequences for adequate longitudinal assessment of "pharyngeal" surgical treatment outcomes in future studies.

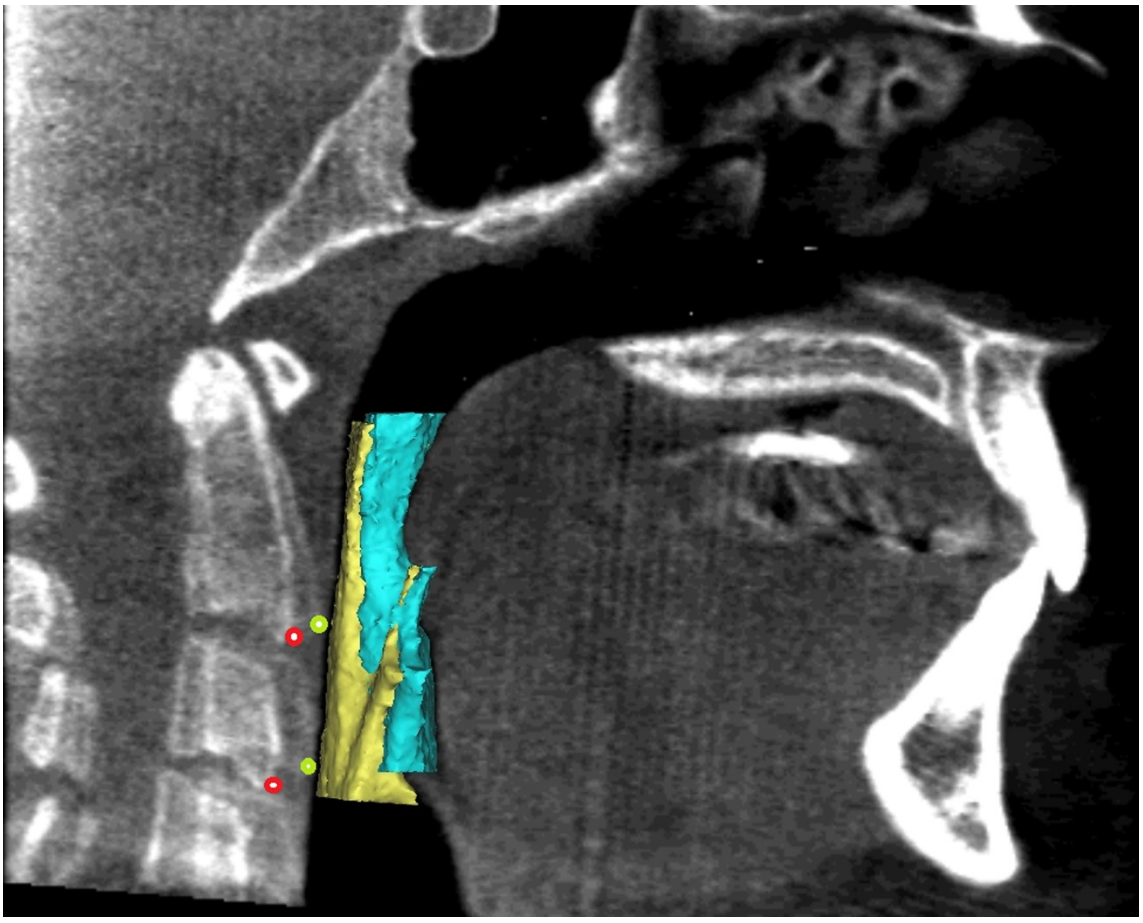


Figure 4.6: Large distances between C2 and C3 with large airway model discrepancies. T1 and T2 registered mid-sagittal CBCT image for subject 1 with neck flexion. Green points: C2-C3 at T1, Red points: C2-C3 at T2, blue airway: at T1, yellow airway: at T2.

Stratemann et al[18] non-rigidly transformed 30 upper airway surfaces to that of one subject by embedding 27 landmarks in each airway. The resultant analysis was in the format of color map. This registration method is computationally costly, the 3D models are deformed, and lacks quantitative information expressed in x, y, and z axes. One way to accurately assess MEs in a given 3D airway model, is to include each point forming the 3D model (in x, y, and z location) in the coordinate transformation by exporting the data as point clouds. This however is computationally demanding because these 3D models are formed by hundreds of thousands of points. Another option is to use the centers (nodes) of the triangles forming the mesh of a given 3D model. These nodes/points can be used in a sampled point-based analysis representative of the entire 3D models to allow a Cartesian-based quantitative assessment in the xyz axes for a given change, such as that offered by 3-matic® *Part Comparison Analysis* tool.

After coordinate transformation and image registration, the total volume of the upper airway (T1-T2) changed by 25.76±24.9% (2.09±1.95 cm^3) and the total surface area by 13.85±10.8% (4.58±3.95 cm^2). A volume difference of 1 cm^3 (= 1ml) was described as the size of two "standard" sugar cubes. [19, 20] Consequently, surface area change of 7.55 cm^2 is equivalent to the total surface area of two sugar cubes. Using this analogy, the mean change in volume and surface area in this study is estimated to be equivalent to that of 4 and 1.2 sugar cubes, respectively. Conceptually, this would be clinically relevant if such changes occurred in localized/ specific part of the airway. However, volumetric measurement of the upper airway ignores a clinically important factor; distribution. On the other hand, part analysis takes into consideration the amount and distribution of change to produce meaningful results. In this study, the mean part analysis was 0.43±0.3 mm and the largest distances travelled by the triangular

nodes forming the entire airway model were no more than 5 mm in either direction, table 4.5 and Figure 4.4b. These larger differences (> 2 mm; red in positive direction and blue in negative direction) were noted in subjects 1, 5, 7, 8, 9, and 10 in Figures 4.4b and 4.5) and larger volume and surface area changes were noted in subjects 8 and 9, Figure 4.4a. This can be attributed to large C2/C3 inter-landmark distances (> 3 mm post-coordinate transformation) i.e. larger neck flexion in subjects 1, 5, 7, 9, and 10 as noted in the registered blue-purple airway models in Figure 4.5. In fact, significant and strong positive correlation was found between C2-C3 inter-landmark distance and the minimum/maximum part analysis distances, table 4.6. In other words, neck flexion producing > 3 mm inter-distance at C2-C3 (in at least one axis) is likely to produce larger distances between localized parts of the airway models. In contrast, there were negligible-weak correlations between C2-C3 distances and airway volume or surface area. The main purpose of this registration method is to utilize it for longitudinal CBCT image analysis of the upper airway after surgey (e.g. adenotonsillectomy). Thus, adjusting for neck flexion using rigid alignment, based on the cervical vertebrae, would mean distorting the remainder of landmarks. Also, applying deformable alignment would introduce bias in the assessment of the pharyngeal airway that lies in very close proximity to the vertebrae.

In subjects 8 and 9, there was major change in tongue position or tongue curling from T1-T2, causing evident discrepancies in the shape of the airway. This has serious implications to controlling tongue position when assessing airway using longitudinal CBCT images. It is evident that large neck flexion, tongue curling, or swallowing will impact the pharyngeal airway. Using deformable alignment to correct for such positioning errors may introduce bias in the assessment of treatment response. Rather, such errors should minimized by ensuring standard imaging parameters. For example, patients should be instructed to relax the tongue against their anterior

teeth, not to swallow, adjusting head and chin rests of the CBCT unit for proper head position rather than requesting the patient to extend/flex the neck, and finally consider reducing exposure time to reduce chances of motion or heavy breathing.

Limitation to this study is that the sample of 10 subjects in T1-T2 data was randomly chosen from a previous study conducted at our institution. This resulted in a heterogeneous sample of subjects receiving different types of orthodontic treatment (fixed orthodontic brackets, tooth or bone-anchored maxillary expansion). However, this did not appear to impact the results of this current study in which our aim was to present a registration method that can be applied to an orthodontic cohort. Another point to address is the arbitrary nature of the cut-off limits to errors in landmark identification and coordinate transformation (at 1.5 mm), and distances between airway models (at 2 mm). These limits may be considered rigorous especially the one pertaining to airway analysis, as it also take into consideration CBCT errors related to partial volume averaging (±voxel size which in this study equals 0.3 mm) in addition to landmark errors due to intra-examiner variability and coordinate transformation.

Conclusions

Based on the results of this study, the following conclusions can be inferred:

1. Tips of nasal bone and clivus, right and left foramen spinosum and foramen ovale produced reliable landmarks for new coordinate transformation for the purposes of CBCT registration.
2. The described coordinate transformation significantly corrected positioning errors in longitudinal CBCT data, however is unable nor designed to correct for evident neck flexion.
3. Neck flexion producing > 3 mm C2 and C3 inter-distance caused localized airway discrepancies (2 mm > airway part analysis < 5 mm).
4. Similar airway discrepancies were also found, with small C2/C3 inter-distances, in subjects with significant change in tongue position from T1-T2.
5. Controlling tongue position and neck flexion has major implication in future CBCT airway imaging protocol.

4.5 References

1. Alsufyani NA, Al-Saleh MA, Major PW. CBCT assessment of upper airway changes and treatment outcomes of obstructive sleep apnoea: A systematic review. *Sleep Breath.* 2013;17:911-923. doi:10.1007/s11325-012-0799-7; 10.1007/s11325-012-0799-7.

2. Cevidanes LHC, Oliveira AEF, Grauer D, Styner M, Proffit WR. Clinical application of 3D imaging for assessment of treatment outcomes. *Semin Orthod.* 2011;17:72-80.

3. Cevidanes LHS, Styner MA, Proffit WR. Image analysis and superimposition of 3-dimensional cone-beam computed tomography models. *American Journal of Orthodontics and Dentofacial Orthopedics.* 2006;129:611-618.

4. da Motta ATS, Carvalho FAR, Oliveira AEF, Cevidanes LHS, Almeida MAO. Superimposition of 3D cone-beam CT models in orthognathic surgery. *Dental Press Journal of Orthodontics.* 2010;15:39-41.

5. Cevidanes LHC, Motta A, Proffit WR, Ackerman JL, Styner M. Cranial base superimposition for 3-dimensional evaluation of soft-tissue changes. *American Journal of Orthodontics and Dentofacial Orthopedics.* 2010;137:S120-S129.

6. Park S-, Yoon J-, Kim Y-, Hwang D-, Cho B-, Son W-. The evaluation of the nasal morphologic changes after bimaxillary surgery in skeletal class III maloccusion by using the superimposition of cone-beam computed tomography (CBCT) volumes. *Journal of Cranio-Maxillofacial Surgery.* 2012;40:e87-e92.

7. Lagravre MO, Secanell M, Major PW, Carey JP. Optimization analysis for plane orientation in 3-dimensional cephalometric analysis of serial cone-beam computerized tomography images. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontology.* 2011;111:771-777.

8. Lagravère MO, Major PW, Carey J. Sensitivity analysis for plane orientation in three-dimensional cephalometric analysis based on superimposition of serial cone beam computed tomography images. *Dentomaxillofacial Radiology.* 2010;39:400-408.

9. Lagravère MO, Hansen L, Harzer W, Major PW. Plane orientation for standardization in 3-dimensional cephalometric analysis with computerized tomography imaging. *American Journal of Orthodontics and Dentofacial Orthopedics.* 2006;129:601-604.

10. Lagravère MO, Low C, Flores-Mir C, et al. Intraexaminer and interexaminer reliabilities of landmark identification on digitized lateral cephalograms and formatted 3-dimensional cone-beam computerized tomography images. *American Journal of Orthodontics and Dentofacial Orthopedics.* 2010;137:598-604.

11. Lagravère MO, Gordon JM, Guedes IH, et al. Reliability of traditional cephalometric landmarks as seen in three-dimensional analysis in maxillary expansion treatments. *Angle Orthod.* 2009;79:1047-1056.

12. Deeb W, Hansen L, Hotan T, Hietschold V, Harzer W, Tausche E. Changes in nasal volume after surgically assisted bone-borne rapid maxillary expansion. *American Journal of Orthodontics and Dentofacial Orthopedics.* 2010;137:782-789.

13. DeCesare A, Secanell M, Lagravère MO, Carey J. Multiobjective optimization framework for landmark measurement error correction in three-dimensional cephalometric tomography. *Dentomaxillofacial Radiology.* 2013;42.

14. Chen Y-, Chen S-, Yao JC-, Chang H-. The effects of differences in landmark identification on the cephalometric measurements in traditional versus digitized cephalometry. *Angle Orthod.* 2004;74:155-161.

15. Lagravre MO, Gordon JM, Flores-Mir C, Carey J, Heo G, Major PW. Cranial base foramen location accuracy and reliability in cone-beam computerized tomography. *American Journal of Orthodontics and Dentofacial Orthopedics.* 2011;139:e203-e210.

16. Naji P, Alsufyani N, Lagrave`re M. Reliability of anatomic structures as landmarks in three-dimensional cephalometric analysis using CBCT . *Angle Orthod.* 2014;86:000-000.

17. Shibata M, Nawa H, Kise Y, et al. Reproducibility of three-dimensional coordinate systems based on craniofacial landmarks: A tentative evaluation of four systems created on images obtained by cone-beam computed tomography with a large field of view. *Angle Orthod.* 2012;82:776-784.

18. Stratemann S, Huang JC, Maki K, Hatcher D, Miller AJ. Three-dimensional analysis of the airway with cone-beam computed tomography. *American Journal of Orthodontics and Dentofacial Orthopedics.* 2011;140:607-615.

19. El H, Palomo JM. Editor's comment and Q&A: Measuring the airway in 3 dimensions: A reliability and accuracy study. *American Journal of Orthodontics and Dentofacial Orthopedics.* 2010;137:S50-S52. doi:http://dx.doi.org/10.1016/j.ajodo.2010.01.014.

20. Valiathan M, El H, Hans MG, Palomo MJ. Effects of extraction versus non-extraction treatment on oropharyngeal airway volume. *Angle Orthod.* 2010;80:1068-1074.

Chapter 5

Semi-automatic segmentation software for the upper airway

5.1 Ground Truth Delineation for Medical Image Segmentation

5.2 Segmentation of the nasal and pharyngeal airway using CBCT: Part I: A new approach

5.3 Segmentation of the nasal and pharyngeal airway using CBCT: Part II: reliability and validity

5.1 Ground Truth Delineation for Medical Image Segmentation (Based on Local Consistency and Distribution Map Analysis)*

Irene Cheng, Xinyao Sun, *Noura Alsufyani,* Paul Major, Anup Basu
*Published, in part, in the Proceedings of the Annual IEEE Engineering in Medicine and Biology Conference (EMBC) 2015

Preface

This project was a collaboration between the Departments of Computing Sciences and Dentistry at the University of Alberta. I was responsible for the image tracing collection and contributed to concept formation and this chapter's composition. From the Computing Sciences, Dr. Irene Cheng was responsible for the concept and algorithm design. Xinyao Sun was responsible for implementation and statistical analysis. The manuscript was written by Dr. Cheng. Prof. Anup Basu was the co-supervisory author and was involved with concept formation. Dr. Paul Major is the supervising author to this thesis and was involved with concept formation and manuscript composition.

This research project, of which this thesis is a part, received research ethics approval from the University of Alberta Research Ethics Board, Project Name "Automatic Segmentation of the Upper Airway using Cone Beam Computed Tomography: A validation study", Pro00021181, March 16, 2011.

5.1 Ground Truth Delineation for Medical Image Segmentation based on Local Consistency and Distribution Map Analysis

Abstract: The interest in cone-beam computed tomography (CBCT) and its additional benefits to oral and maxillofacial diagnosis and treatment planning is increasing. CBCT generated 3D models, Computer-aided detection (CAD) systems, are the product of segmentation, manual or automatic. Several aspects regarding upper airway segmentation need to be addressed; validity and reliability. In order to assess the accuracy of a CAD segmentation algorithm, a comparison with ground truth data is necessary. To date, ground truth delineation relies mainly on contours that are either manually defined by clinical experts or automatically generated by software. In this paper, we propose a systematic ground truth delineation method based on a Local Consistency Set Analysis approach, which can be used to establish an accurate ground truth representation, or if a ground truth is available, to assess the accuracy of a CAD generated segmentation algorithm. We validate our computational model using medical data. Experimental results provides consistency information at pixel level, and thus is invariant to global compensation error.

5.1.1 Introduction

Accuracy and reliability of airway measurements in CBCT images have been tested, in the dental literature, using linear, cross-sectional areas, and volume (systematic reviews in Chapter 2). In image segmentation, however, detecting the contour or boundary of the object of interest is an important step as the segmented structure is then reconstructed into a 3D model that is essential for many clinical applications to aid in diagnosis, treatment planning, and assess treatment outcomes more efficiently by the medical image.

The precision of many of newly proposed techniques and algorithms used for automatic detection and segmentation[1-3] needs to be compared with the manual detection by an expert. This, however, needs to be preceded by evaluating the ground truth that is defined by the professional experts.

Generally there are two different methods to measure the accuracy of Ground Truth. One is the artificial approach[4] using the synthetic images (phantoms) in which definition of ground truth is fairly easy however does not reflect the reality in true medical image. The other is manually annotated approach[5] which is "based on the assumption that the precision and reliability of existing automatic techniques is vastly inferior to human interpretation"[6]. The latter is the most common and widely accepted approach for performance characterization.

Nonetheless, manual ground truth is not faultless due to intra- or inter-examiner errors. The main aim of this work is to test the consistency of single expert's manual tracing of the upper airway, thus testing consistency of the "ground truth".

5.1.2 Methods

Image Selection

Five CBCT image sets of adolescent subjects were randomly and retrospectively selected from the Orthodontic Graduate clinic database at the University of Alberta. The images were acquired by the Classic iCAT CBCT scan (Imaging Sciences International, Hatfield, PA). Images were acquired with 120 kVp, 24 mAs, and 0.3 mm voxel size. For each image set, six sections were selected and exported as JPEG files:

1) Axial section through the inferior anterior point of the second cervical vertebrae, C2.
2) Axial section through the inferior point of the anterior arch of the first cervical vertebrae, C1.
3) Axial section through the inferior point of Clivus.
4) Coronal section through the posterior nasal spine, PNS.
5) Coronal section through the Crista galli; of ethmoid bone.
6) Coronal section through the tip of nasal bone.

Image sections 1, 2, and 3 represent pharyngeal airway and sections 4, 5, and 6 represent nasal airway. Using a tracing program (TRACER A, developed at the Department of Computing Sciences, University of Alberta), one examiner (PhD student) traced the airway boundaries in all images sections (single airway region in sections 1-3 and bilateral airway region in sections 4-6, i.e. nose) three times. The total is 45 airway regions, each region has 3 boundary data point sets saved as text files (.txt) containing x and y coordinated of each tracing point.

Tracing Evaluation

For the same region within one image, the three tracings are called *A*, *B, C*. All are discrete 2D points with (*x*, *y*) identifying its location. The coordinate system of each image is static and the original point (0, 0) located at left bottom of the image during each tracing attempt. Therefore, the first evaluation phase tests the consistency between these three points data set relative to the (0, 0) point. If there is one point *PA* belongs to *A*, we can find one point *PB* from *B* and stratified the condition as $\{SDistB(PA) : min|PAPB|, PA\varepsilon A, \exists PB\varepsilon B\}$ to go through all the points from *A* and obtains shortest distance *SDist* for each point. According to the distance distribution, smaller distances between points from *A* to *B* represent high consistency.

Next phase is data classification, the calculation from phase 1 is applied to all pairs among *A*, *B, C*. Following, we define a tolerable error at 3 pixel distance (in this study =0.9 mm as pixel size is 0.3 mm) thus tolerable error. Therefore, any point with $SDist \leq 3$ will be treated as consistent to the target points set as the "Real Positive" points.

The final phase is data analysis after collecting all the Real Positive points for each data set based on itself and target to other two data sets. The Consistent level calculates correlations among all three points from *A*, *B, C.* If a point in one tracing has less than 3 pixel distance to the other two tracings, the correlation is high. A correlation of 1 represents perfect overlap and 0 pixel distance between tracings, i.e. high consistency.

5.1.3 Results

After applying the consistent level elevation on the 45 airway regions, the outputs distribution are presented in Figure 5.1.1.

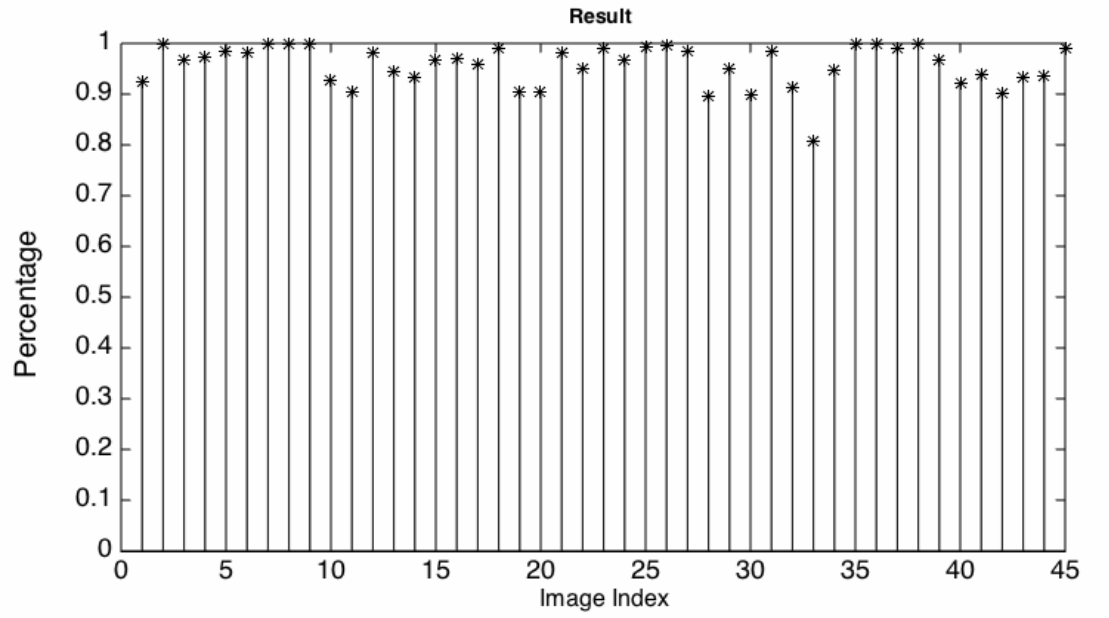


Figure 5.1.1: Consistency level of 45 airway regions.

Consistency levels ranged between 0.80 to 1, and most airway regions presented with consistency levels ≥ 0.9 except for two images. Examples of high consistent level cases with its raw tracing image are presented in Figure 5.1.2.

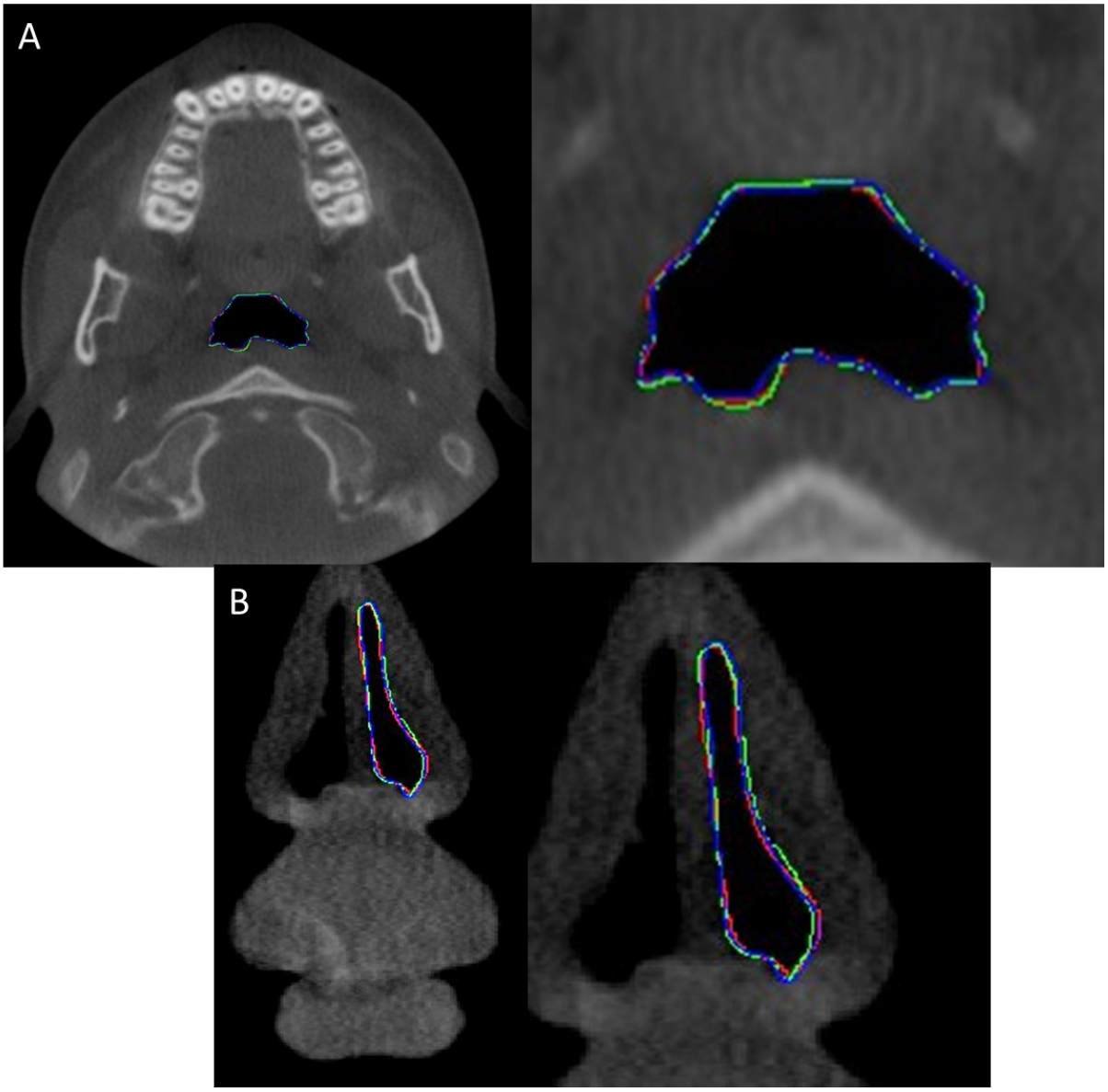


Figure 5.1.2: CBCT image sections showing high consistency level tracing (=1). A) Axial section and its close-up of the pharyngeal airway. B) Coronal section and its close-up of the nasal cavity.

Examples of low consistent level cases with its raw tracing image are presented in Figure 5.1.3. More tracing examples are provided in Appendix B.

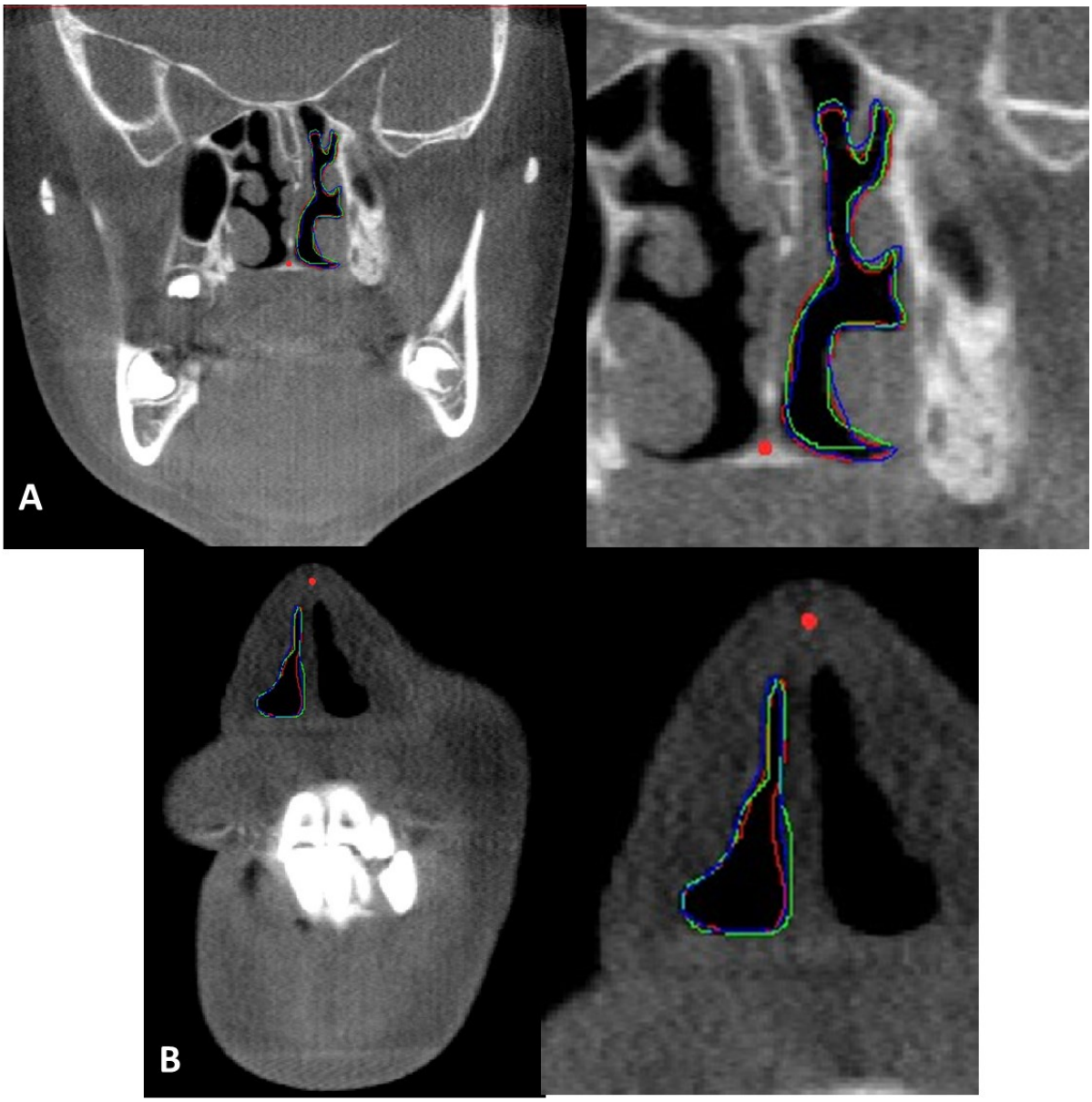


Figure 5.1.3: CBCT image sections showing lowest consistency level tracing. A) Coronal section and its close-up of the posterior nasal cavity, consistency level =0.80. B) Coronal section and its close-up of the anterior nasal cavity, consistency level =0.89.

Two additional graphs are provided for the images with highest consistency levels (Case 1) and for the lowest (Case 6), Figures 5.1.4 and 5.1.5, respectively. Distance circle graph shows the *SDist* of points from the base data set to the target data set, which is represented by the distance

from each points on the graph to the original point. The normalized *SDist* distribution bar indicates the distances distribution of the base data set to the target data set.

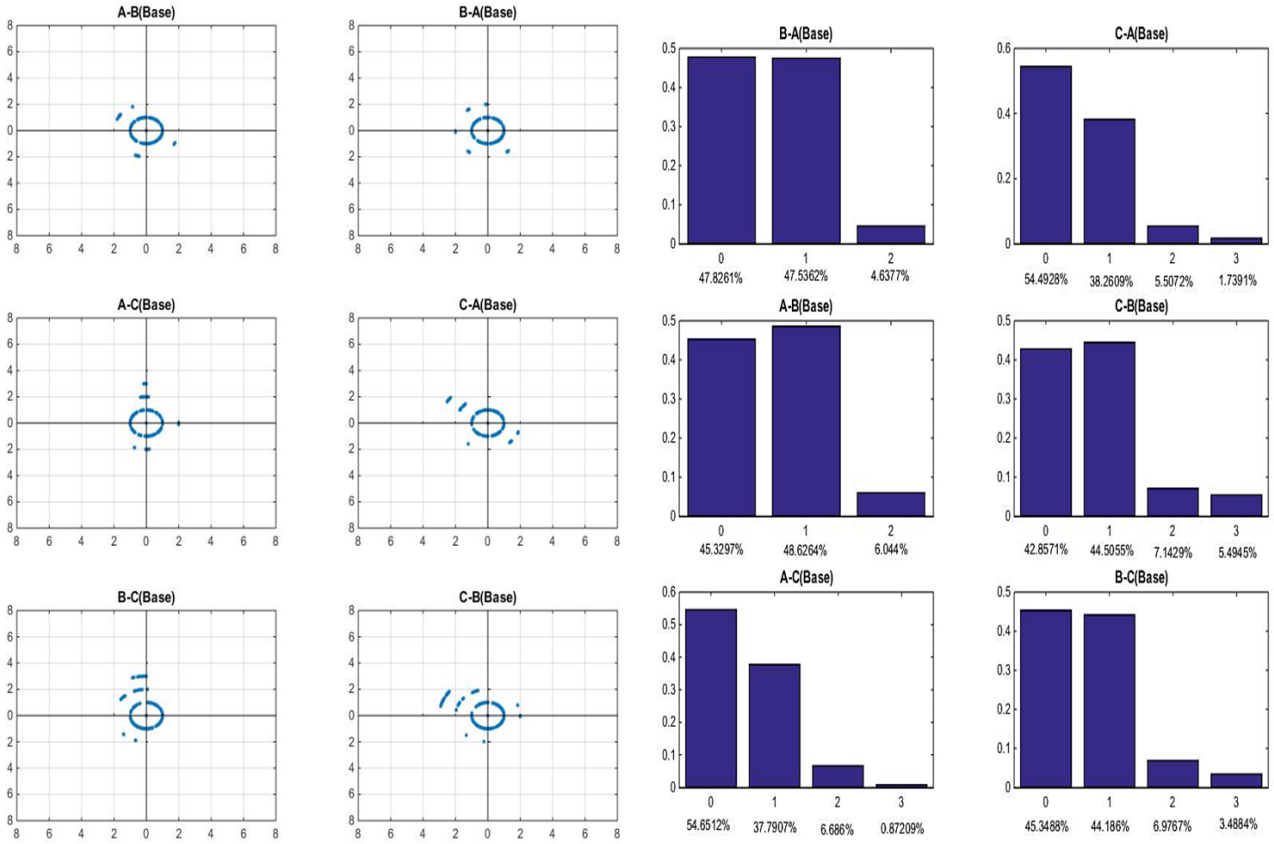


Figure 5.1.4: Distance circle (left) and distribution bar (right) graphs of Case 1.

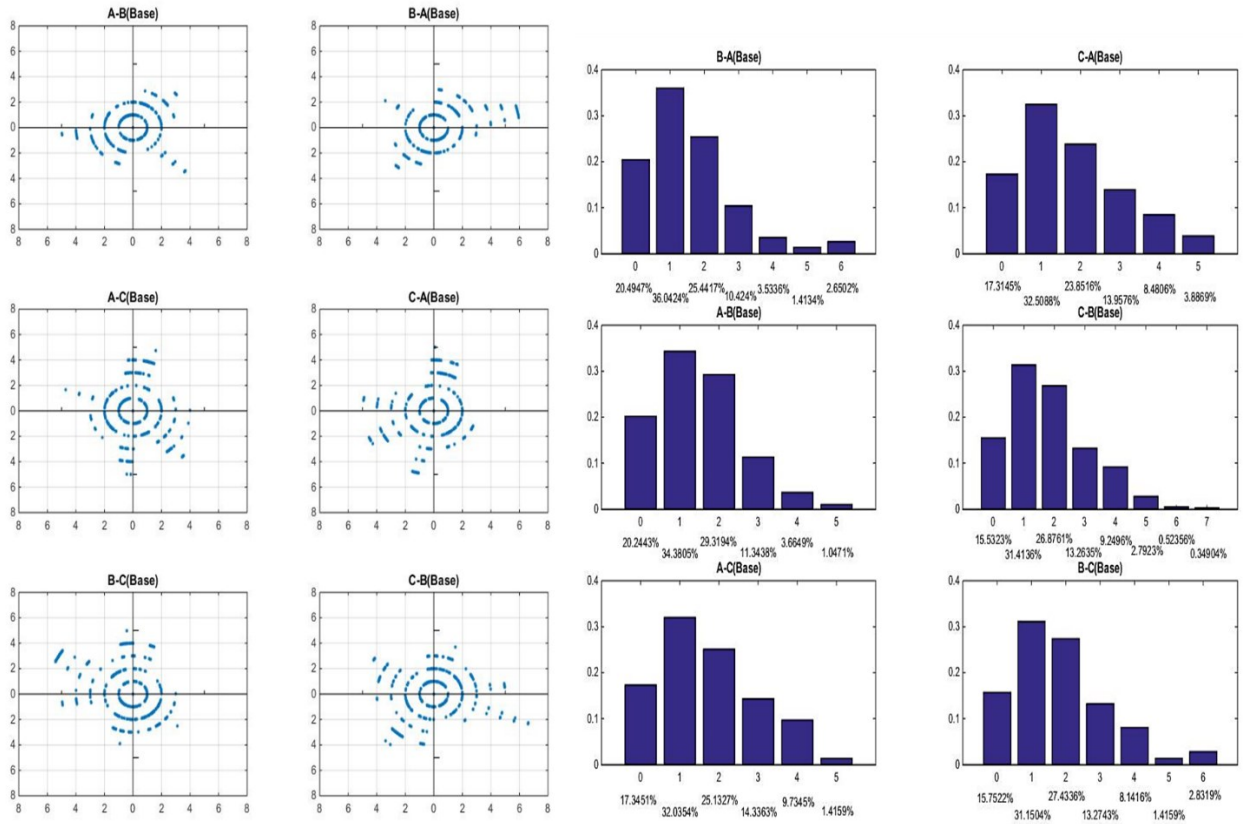


Figure 5.1.5: Distance circle (left) and distribution bar (right) graphs of Case 6.

By comparing the two extreme cases, it is apparent from the distribution graphs, Figures 5.1.4 and 5.1.5, that the *SDist* of most tracing points in Case 6 was ≤ 3 pixels with few points > 3 pixels, whereas in Case 1 there were no points with *SDist* >3.

Conclusion

Although it is impossible for an examiner to identically trace the same boundary twice, evaluating the different tracing groups in this work shows that the expert's tracings of 45 upper airway images, three times, were of high consistency (no more than 3 pixels) and therefore accepted as "reference" in upcoming studies.

5.1.4 References

1. Zenzo S. A note on the gradient of a multi-image. , computer vision, graphics and image processing. . *Computer Vision, Graphics and Image Processing.* 1986;33:116-125.

2. Lee H, Cok D. Detecting boundaries in a vector field. *IEEE Trans on Signal Processing.* 1991;39 (5):1181-1194.

3. Scharcanski J, Venetsanopulos A. Edge detection of color images using directional operators. *IEEE Transactions on Circuits and Systems for Video Technology.* 1997;7 (2):397-401.

4. Wenyin L, Dori D. A protocol for performance evaluation of line detection algorithms. *Machine Vision and Applications.* 1997;9 (5-6):240-250.

5. Heath M, Sarkar S, Sanocki T, Bowyer K. Comparison of edge detectors: A methodology and initial study. *Computer Vision and Image Understanding.* 1998;69 (1):38-54.

6. Hoover A, Jean Baptiste G, Goldgof D, Bowyer K. A methodology for evaluating range image segmentation techniques. University of South Florida: Department of Computer Science; 1995;Technical Report 9501.

5.2 Segmentation of the nasal and pharyngeal airway using cone beam computed tomography Part I: A new approach*

NA Alsufyani, A Hess, N Ray, PW Major
*Submitted to Oral Radiology

Preface

This project was a collaboration between the Departments of Computing Sciences and Dentistry at the University of Alberta. I was responsible for the concept formation, data collection and analysis, and manuscript composition. From the Computing Sciences, Andy Hess was responsible for the concept formation, algorithm configuration, and assisted in data collection and analysis, and manuscript composition. Dr. Ray (from Computing Sciences) and Dr. Major (from Dentistry) were the supervisory authors and were involved with concept formation and manuscript composition.

This research project, of which this thesis is a part, received research ethics approval from the University of Alberta Research Ethics Board, Project Name "Automatic Segmentation of the Upper Airway using Cone Beam Computed Tomography: A validation study", Pro00021181, March 16, 2011.

5.2 Segmentation of the nasal and pharyngeal airway using cone beam computed tomography Part I: A new approach

Abstract

Objectives: to develop a semi-automatic segmentation program that efficiently and accurately segments the upper airway structure from cone beam computed tomography (CBCT) images into a 3D model. **Methods:** Local Decomposition Gradient Segmentation (*LEDGES*) algorithm is applied in a software package, Segura©, developed to segment the upper airway using the CBCT data of one subject. Then, four generic syringes (1, 3, 10, and 60 ml) were scanned with CBCT, The air inside the syringes was segmented, and reconstructed into 3D models. The segmentation process was repeated five times and the syringe volumes were measured to test the software's reliability. The accuracy of Segura© was tested by comparing the known volumes of the four syringes to the calculated syringe volumes from their Segura© segmented 3D models. Using the CBCT of the subject sample, the time to segment the upper airway using Segura© was compared to that of manual segmentation to test time efficiency. **Results:** Implementing LEDGES in Segura© software allowed easy and efficient segmentation of the upper airway (nasal and pharyngeal) in the sample CBCT. The volumes of Segura© segmented 3D models were reliable (standard deviations $\leq$ 0.11 ml) and accurate (intra-class correlation coefficient= 100%, CI 97-100%). Segmentation with Segura© was 26 times less than manual segmentation for the same image set. **Conclusion:** Preliminary trials of Segura©, and the results thus obtained are very promising from time efficiency, reliability and accuracy perspectives. Forthcoming work entails detailed validation of *Segura*© using human upper airways from CBCT scans.

5.2.1 Introduction

Three-dimensional (3D) models of the upper airway segmented from Cone-beam computed tomography (CBCT) scans are emerging as means to visualize and assess the upper airway. Such imaging techniques provide significant insights into the anatomy of the upper airway especially in subjects with sleep disordered breathing.[1] Segmentation refers to the extraction of structural information of particular interest from surrounding images for visualization or characterization of anatomy or pathology.[2] Generally, segmentation methods can be broken down into three main types: manual, semi-automatic and automatic.

Manual segmentation is the most accurate method as it allows for the most operator control however is significantly time consuming.[3, 4] Commercial software products allow automatic segmentation of the upper airway by means of global thresholding. This method relies on setting an intensity range (grey-threshold) such that voxels having intensity values outside that range are set to zero. This provides fast, but potentially inaccurate segmentation.[3, 5] Semi-automatic methods are classified according to three main approaches: global filtering, region growing and model-based methods.1 Automatic segmentation of the nasal cavity is rarely attempted in the dental literature.[6] In the otolaryngology literature, it was reported that semiautomatic segmentation took 3.5 hours for detailed segmentation of nasal/paranasal airway compared to 8–16 hours of manual segmentation, which is still time consuming, not as accurate as manual segmentation, and not feasible in clinical or research workflow.[4, 5, 7] The varying densities of bone, mucosa or air in the upper airway renders the segmentation process very difficult and revealed the limitations of traditional segmentation approaches, such as region growing.[8]

Changes in the geometric features of the upper airway are imperative to assess patient response to surgical treatment in the sleep disordered breathing population. Taking into account the suboptimal image resolution of CBCT images compared to MDCT, the complex anatomy of the nasal cavity, heterogeneity of grey-level throughout the upper airway, and realistic segmentation time instigate the need for a semi-automatic method that better defines relevant intensity values and allows for limited user input.

The purpose of this paper is to develop an accurate, reliable, and time efficient semi-automatic segmentation program specific for the upper airway to generate a realistic patient-based 3D mesh model.

5.2.2 Methods

CBCT protocol

The CBCT image set of one subject was randomly retrieved from the Graduate Orthodontic clinic database, department of Dentistry, University of Alberta. The images were acquired using the Classic iCAT CBCT scan (Imaging Sciences International, Hatfield, PA). CBCT protocol used a medium-large field of view (16 cm width x 13 cm height), 120 kVp, 24 mAs, 20 seconds scan time, and 0.3 mm voxel size. This image set was used to develop and test the segmentation program.

Semiautomatic Segmentation:

The Local Decomposition Gradient Segmentation "LEDGES" algorithm

Using the CBCT image volume, the automatic segmentation of local regions was defined around seed points that were manually supplied by the user or automatically generated by

previously-segmented adjacent cross-sections. The *LEDGES* algorithm automatically searches for the optimal local segmentation around each point by first representing each local image by the local threshold decomposition[9] which contains the point, Figure 5.2.1.

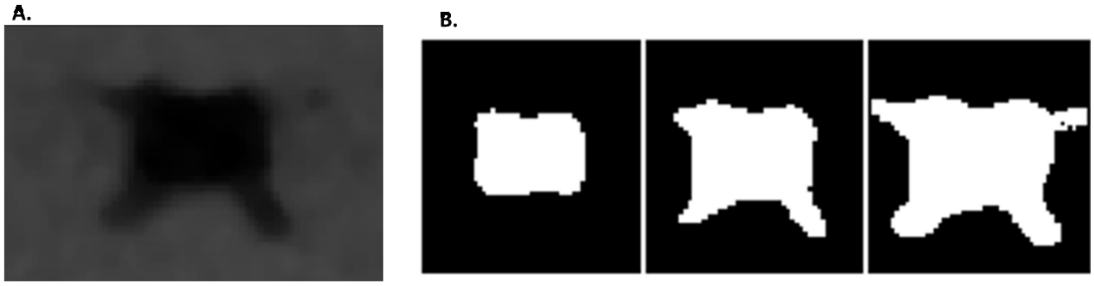


Figure 5.2.1. Threshold Decomposition. (A) Original image. (B) Binary images Ik for k = 15, 33, 50

Following the method described by Saha and Ray[10], the image gradient of each binary image of this decomposition was then used to sample the original image, Figure 5.2.2 and the mean value calculated. The optimal local segmentation was considered to be the cross-section corresponding to the maximum mean value, Figure 5.2.3.

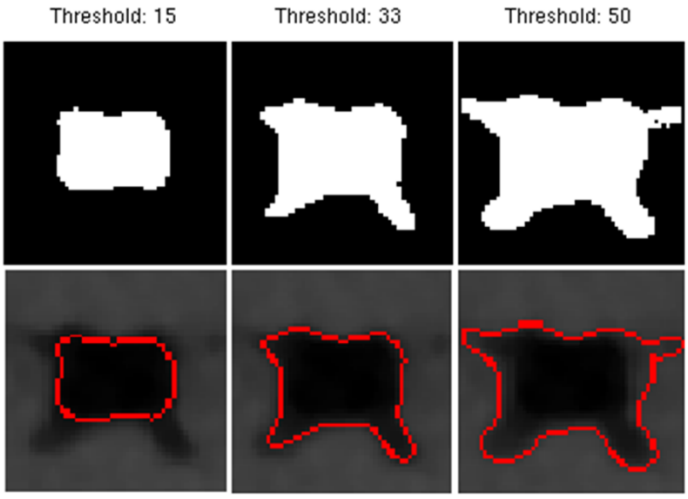


Figure 5.2.2: Image gradient. Each binary image IK corresponds to an image gradient that is used to sample the original image. Red points denote the origin of each gradient vector.

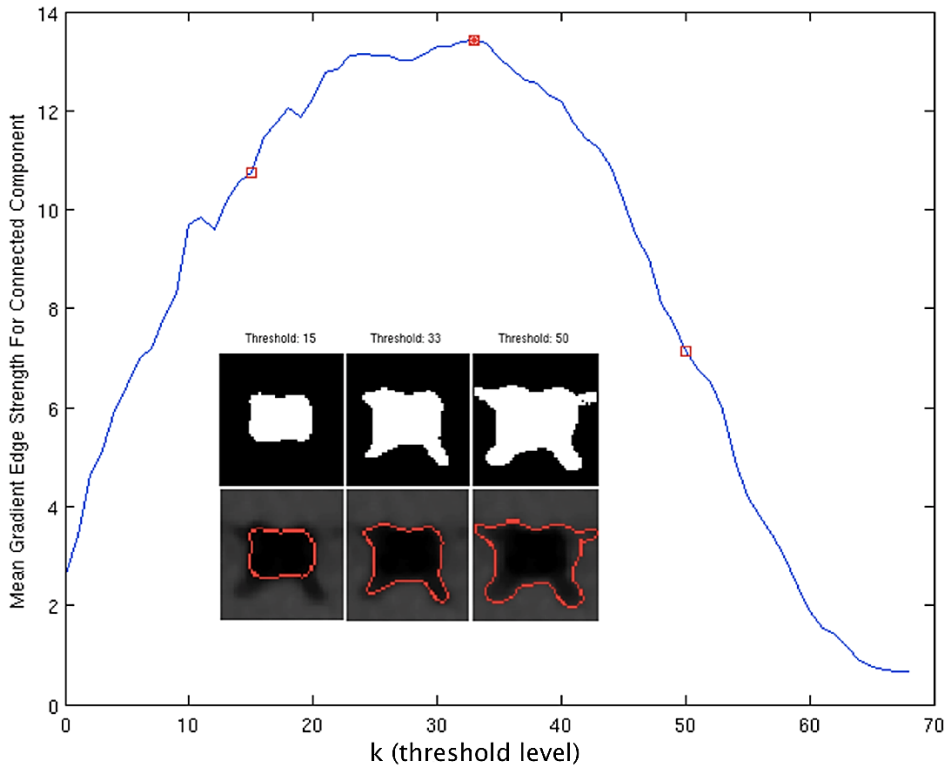


Figure 5.2.3: Optimal segmentation: corresponds with the k value where the maximal mean gradient occurs (k = 33).

Any image I, of bit depth d, can be thresholded by a value k where $0 <= k < 2^d$ (i.e. d=8 means 256 values). Each threshold value k produces a binary image $I_k = \{I <= k\}$ with value 1 at pixels where the image is less than k, 0 otherwise. The set of all I_k (for each k) is the *threshold decomposition* of the image I, denoted here as $D_s = \{I_k$ such that $0 <= k < 2^d\}$, Figure 5.2.1. Each seed point s, corresponding to the user clicking on the image, is associated with a local region where this decomposition can be performed locally, namely the *local threshold decomposition* D_s. Since every I_k in D_s can contain multiple connected components, every I_k retains only those connected components that contain s. For each I_k in D_s, we consider its corresponding image gradient G_k and use these to sample the original image, Figure 5.2.2. The mean value of all these sampled image gradients gives a final number g_k, which represents the

edge strength of I_k, when overlaid over I, and corresponds to the mean change in image pixel values along gradient directions. The threshold value K_s (around each clicked seed point), associated with the largest mean gradient value then corresponds to the optimal segmentation of I around seed point s, Figure 5.2.3. Finally, we consider the optimal segmentation to be the edge set of the union of I_K over all seed points, Figure 5.2.4. The edge set is the set of pixels of value 1 found on the edge of all connected components in a binary image. The union of binary images is the logical-or of binary images values that combines the pixels of value 1 together into one binary image.

```
for each clicked seed point s (with associated local region):
  compute D_s := {I_k such that 0 <= k < 2^d}, the local threshold decomposition
  retain only connected components of each I_k that contain s
  for each k, 0 <= k < 2^d
    compute G_k, the image gradient of I_k
    g_k = mean(I(G_k))
  end
  M_s = the k value where the maximum g_k occurs
end
segmentation = edges(Union_s(M_s))
```

Figure 5.2.4: The LEDGES algorithm.

Once all cross-sections have been segmented, they are combined into a final 3D mesh using iso2mesh[11] and CGAL[12] and saved to steriolithographic file[13] (.stl). This mesh can then be loaded into other 3D software packages for mesh smoothing, trimming, visualization, or further analysis.

Implementing LEDGES in The Segura© software package

To efficiently segment the upper airway and generate a 3D model, a custom-written program was created using MATLAB® (MATLAB R2012b, The Mathworks Inc., Natick, MA) and the *LEDGES* method was implemented. This software package is referred to as *Segura©*.

Once the DICOM files are loaded into Segura©, the user first defined the region of interest (ROI) on the sagittal section thus defining a series of square, path-orthogonal 2D cross-sections. As such, these exhibit a higher degree of continuity from the hypopharynx to the tip of the nose (compared to axis-aligned cross-sections), eliminate the need to merge segmentations from multiple paths, and specify a more natural segmentation workflow as though "moving through the path", Figure 5.4.5. The semi-automatic segmentation of each of these cross-sections is performed by simply applying the *LEDGES* algorithm to each “seed point”. To further increase workflow speed, these points can be copied and/or automatically generated based on adjacent segmentations from one cross-section to the next.

Segura© also allows for voxel-level image adjustments to adjust for noise, mucous, or seal off regions where segmentation is not desired (e.g. connections to sinuses). Other *Segura©* features (beyond the scope of this paper) allow for efficient segmentation workflow. Once each cross-section has been segmented, they are combined into a final 3D reconstruction of the ROI, Figure 5.2.5.

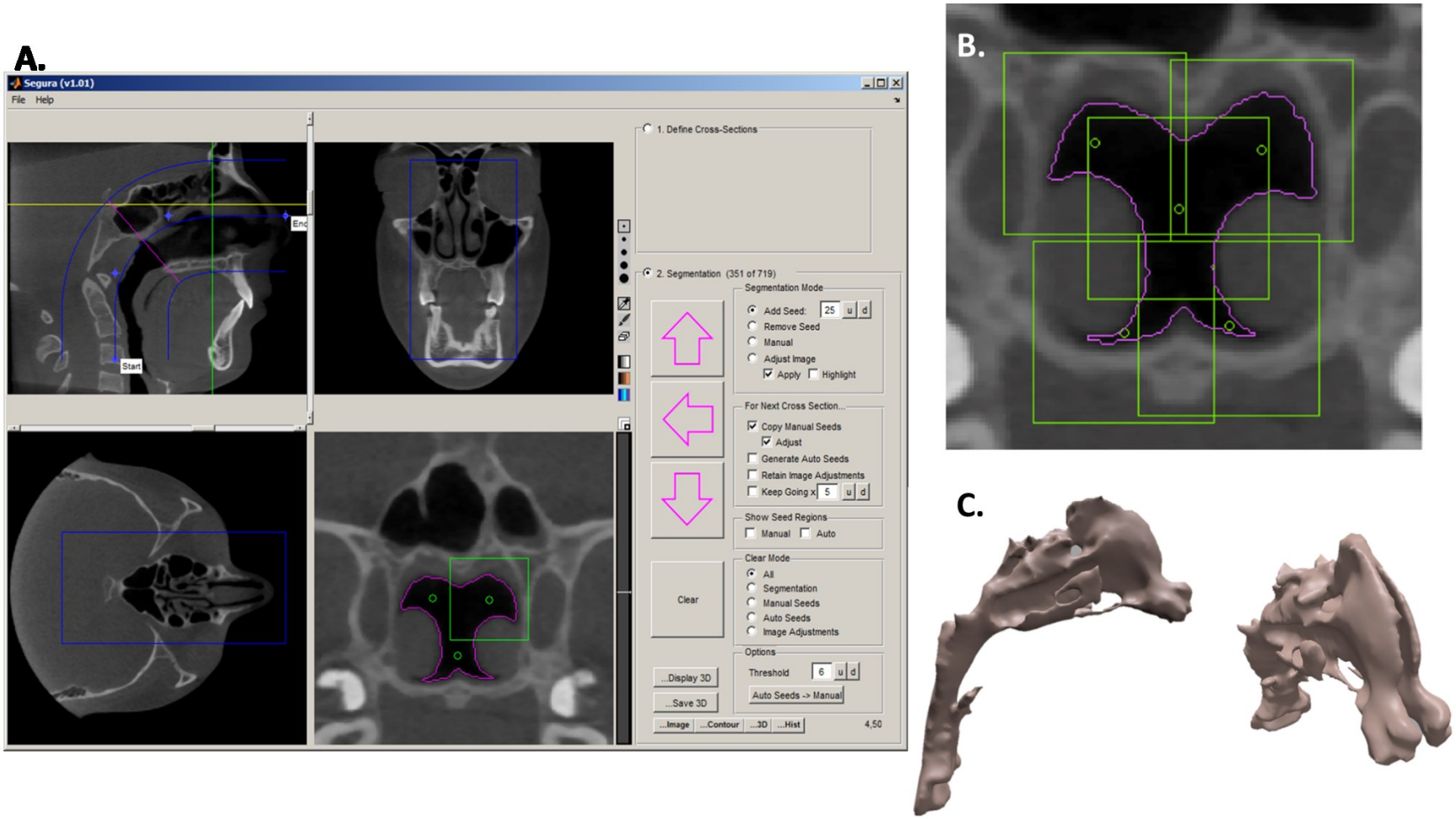


Figure 5.2.5: The Segura© software package. (A) A snapshot of the user interface showing the Region of interest (blue), cross-section view with seed points (green) and current segmentation (magenta). (B) Magnified cross-section image showing local regions (green squares) associated with each seed point within which LTD occurs. (C) Sagittal and angled views of the resultant 3D upper airway model.

Testing *Segura*©:

Reliability and accuracy

To assess the reliability and accuracy of the segmentation of Segura©, four generic (needleless) syringes were imaged with CBCT using the same parameters described in section 1 of the methods. The generic plastic syringes (volumes 1, 3, 10, and 60 ml) were fixed to a block of foam and placed in a plastic container surrounded by 1 inch of water, to mimic soft tissue attenuation, Figure 5.2.6. The resultant DICOM image files were imported into Segura©, semi-automatically segmented then reconstructed into 3D models, five times, by the principal investigator (PI). The resultant 3D models were then exported as .STL models into 3-matic3® [3-matic 7.0, Materialise NV, Leuven, Belgium].

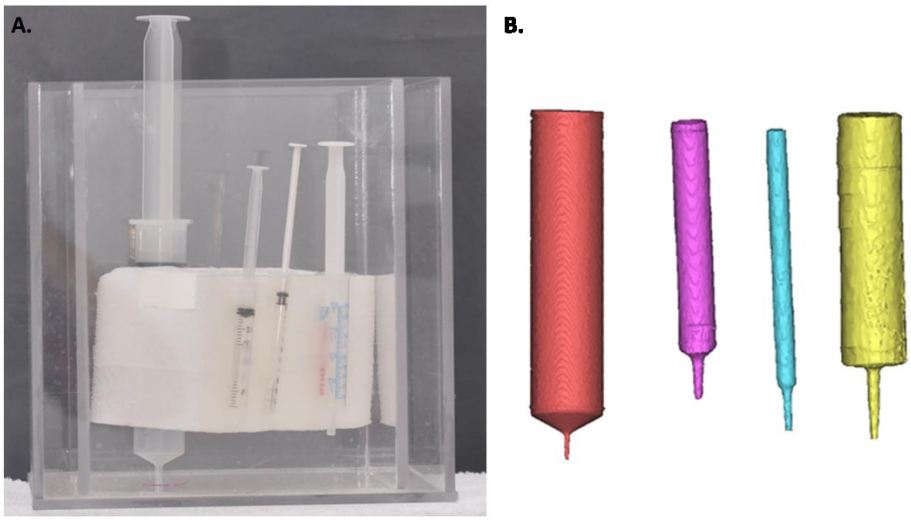


Figure 5.2.6: Generic syringes used to test segmentation of Segura© (A) The syringes in plastic container, (B) Segura© segmented 3D models of the syringes.

Reliability will be assessed by comparing the means and standard deviations of the five trials for each syringe size. To assess accuracy, intra-class correlation coefficient ICC was

calculated between the ground truth, i.e. the known volumes of each syringe and the mean volume calculated from Segura© generated 3D models of the syringes.

Time efficiency

The upper airway of the image sample was segmented manually and semi-automatically and segmentation time recorded to assess time-efficiency. The region of interest included the pharyngeal and nasal airways, maxillary, sphenoid, and ethmoid sinuses. The inferior extent of the ROI was the most anterior-inferior point of the body of the third cervical vertebra, and the superior extent was the last axial image slice intersecting with the planum sphenoidale, Figure 5.2.7.

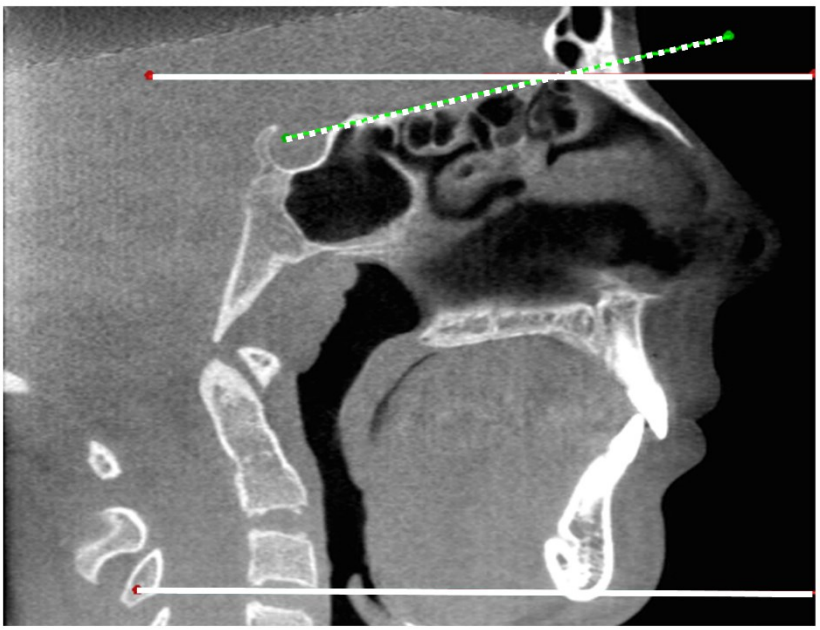


Figure 5.2.7: Mid-sagittal CBCT image showing the upper airway Region of interest (ROI). Dashed line runs through planum sphenoidale and two solid white lines mark the ROI boundaries; inferiorly through the third cervical vertebra and superiorly intersecting with the dashed line.

Manual segmentation was completed using the *Mask tool* in Mimics® software [Mimics 15.0, Materialise NV, Leuven, Belgium], the PI manually selected the grey-level threshold on each axial slice for the entire ROI (~430 slices, 0.3 mm slice thickness, 0 mm inter-slice

interval). The PI adjusted the mask by erasing or adding to the highlighted airway on each slice. Once the upper airway was defined and edited, a 3D model of the mask was created and saved in an ASCII STL format. Using the same sample image, the PI initiated seed-points in Segura© in the most inferior axial slice in the ROI then allowed the seed-points to automatically copy and adjust as the slice moved superiorly within the ROI. The PI was allowed to adjust the seed-points and edit the boundaries of segmentation if needed. Once the upper airway was defined and edited, a 3D model of the segmented ROI was created and saved in an ASCII STL format.

5.2.3 Results

The air volumes of each syringe calculated from Segura© 3D models were consistent between the five trials for all syringe sizes, as evident by the small standard deviations (≤0.11 ml), table 5.2.1. The mean air volumes, from Segura© 3D models, were no more than 0.1-0.2 ml different (less) than the true volume of each syringe, table 1. In addition, the ICC was high, 100% (95% confidence interval= 97-100%), showing that 3D models generated from Segura© are precise.

Table 5.2.1: Volumes of Segura© segmented 3D models vs. true syringe volumes (ml)

	Volumes of Segura© segmented 3D models (ml)*			
True Syringe volumes	Minimum	Maximum	Mean	Std. Deviation
syringe_1ml	0.91	0.93	0.92	0.01
syringe_3ml	2.85	2.88	2.86	0.01
syringe_10ml	9.78	9.83	9.80	0.02
syringe_60ml	59.71	59.98	59.90	0.11
*Volumes represent all five trials				

Using the CBCT data of the sample subject, manual segmentation was completed in 24 hours (1440 minutes) whereas, for the same ROI, segmenting with Segura© took 55 minutes i.e. 26 times less. The resultant 3D models, from manual segmentation and Segura©, appear similar, Figure 5.2.8.

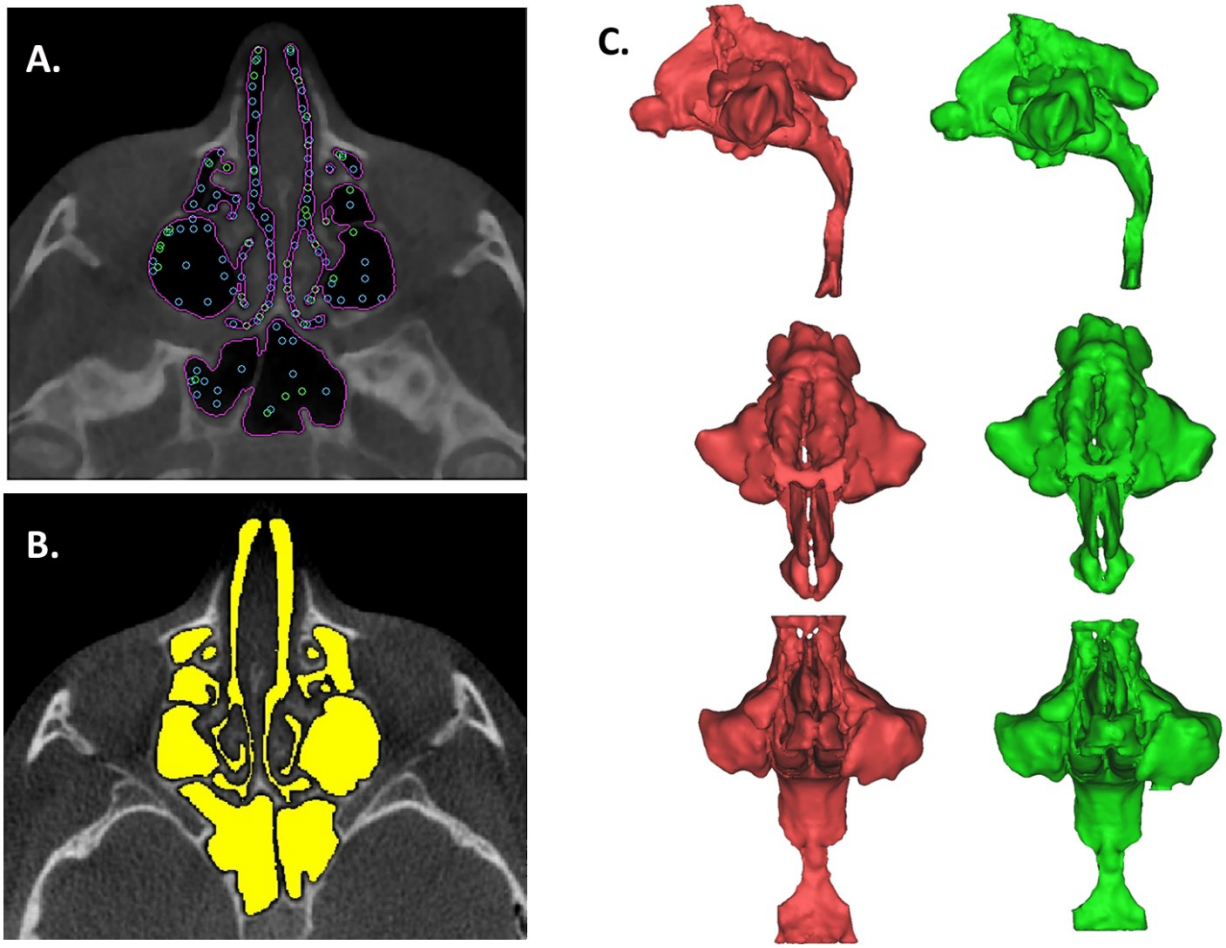


Figure 5.2.8: Upper airway segmentation and 3D reconstruction. (A) Axial CBCT image through the ethmoid air cells showing Segura© seed-points (B) Axial CBCT image comparable to (A) showing highlighted manual segmentation (c) 3D reconstruction of the upper airway from manual segmentation (red) and Segura© (in green.)

5.2.4 Discussion

Although recent work has been directed to validating commercial software products in CBCT airway segmentation, these were limited to the pharyngeal airway with or without the inferior nasal meatus.[6, 14, 15] Reasonably, the nasal cavity is very complex anatomically and challenging due to the presence of mucous thickening or secretions. As such, global thresholding will compromise the segmentation accuracy as the grey threshold of the airway differs within one image slice and between sequential slices of the nasal cavity, and obviously between the nasal cavity and pharyngeal airway. In this work, the LEDGES algorithm "customizes" the segmentation locally within a single image and between sequential image slices in a given image volume.

Implementing LEDGES in Segura© seed points allowed continuous segmentation of the pharyngeal airway as well as the challenging anatomy of the nasal cavity. The seed points were automatically and fairly accurately copied from one slice to the next and it was easier for the user to adjust the presence or location of a seed-point within a given 2D slice than to edit (erase or add) the entire boundaries of the grey-threshold selected in manual segmentation.

The air volume of the 3D models generated by Segura© was reproducible between the five trials for all syringe sizes, as evident by the small standard deviations (no more than 0.11 ml), table 5.2.1. The mean air volumes, from Segura© 3D models, were ≤0.1-0.2 ml compared to the gold standard, i.e. the known volumes of each syringe in table 5.2.1, and high ICC (100%; CI 97-100%) showing that 3D models generated from Segura© are precise, These preliminary results show that Segura© is both reliable and accurate.

In terms of time efficiency, manual segmentation of the nasal and pharyngeal airways of one subject was completed in 24 hours (1440 minutes) whereas, for the same ROI, segmenting with Segura© took 55 minutes i.e. 26 times less. The time of manual segmentation, 24 hours, is more than the 16 hours reported by Tingelhoff et al.[5] is attributed to the fact that we included the pharyngeal and nasal airway to the tip of the nose (anterior nasal nares) where less signal to noise ratio is evident thus representing challenges in segmentation. We also used cone beam CT; suboptimal resolution when compared to spiral CT, and with 0.3 mm slice thickness unlike Tingelhoff et al's 1mm slice thickness.

Majority of the segmentation time, for both segmentation methods, was spent in the anterior nasal nares where low signal to noise ratio is noticeable and in the complex anatomy of superior nasal meatus and ethmoid air cells. The resultant 3D models from manual segmentation and Segura© are very similar, Figure 4.2.8.c.

Several artifacts (e.g. beam hardening, scatter, noise, exponential edge gradient effect, aliasing, partial volume effect, and object motion) and artifact-inducing factors (e.g. scan field, voxel size, and dental material type) are known to hinder the quality of CBCT images.[16, 17] Their impact on the image gradient and subsequent segmentation threshold value and accuracy are beyond the scope of this study however must be considered in future work.

Conclusion

Accurate and detailed segmentation of the complex structures of the nasal and pharyngeal airway is time consuming to be of practical use in clinical or research workflow. We present a new segmentation algorithm (LEDGES), implemented in a new software package *Segura*©, and

used it to segment the complete upper airway of one subject. Results show that segmentation time with Segura© is 26 times less than manual segmentation for the same image set without compromising accuracy or reliability. This dramatic reduction in segmentation time (less than one hour of operator time per subject), makes detailed 3D analysis of the nasal cavity and pharyngeal airway possible for research or clinical practice. Forthcoming work entails validation of *Segura*© using human upper airway CBCT scans and detailed analysis of the reconstructed 3D airway models.

5.2.5 References

1. Perchet D, Fetita C, Prêteux F. Three-dimensional reconstruction of upper airways from MDCT. *Proceedings of SPIE - The International Society for Optical Engineering.* 2005;5672:212-223 Accessed 3 October 2013.

2. Pham D, Xu C, Prince J. Current methods in medical image segmentation. *Annual review of biomedical engineering.* 2000;02:315-37.

3. El H, Palomo JM. Measuring the airway in 3 dimensions: A reliability and accuracy study. *American Journal of Orthodontics and Dentofacial Orthopedics.* 2010;137:S50.e1-S50.e9.

4. Pirner S, Tingelhoff K, Wagner I, et al. CT-based manual segmentation and evaluation of paranasal sinuses. *European Archives of Oto-Rhino-Laryngology.* 2009;266:507-518.

5. Tingelhoff K, Moral AI, Kunkel ME, et al. Comparison between manual and semi-automatic segmentation of nasal cavity and paranasal sinuses from CT images. *Annual International Conference of the IEEE Engineering in Medicine and Biology - Proceedings.* 2007:5505-5508 Accessed 30 January 2013.

6. Alsufyani NA, Flores-Mir C, Major PW. Three-dimensional segmentation of the upper airway using cone beam CT: A systematic review. *Dentomaxillofacial Radiology.* 2012;41:276-284.

7. Salah Z, Bartz D, Dammann F, Schwaderer E, Maassen MM, Straßer W. A fast and accurate approach for the segmentation of the paranasal sinus. *Informatik aktuell.* 2005:93-97 Accessed 9 October 2013.

8. Seo A, Chung SK, Lee J, Kim J-, Kim H. Semiautomatic segmentation of nasal airway based on collaborative environment. *Proceedings - 2010 International Symposium on Ubiquitous Virtual Reality, ISUVR 2010.* 2010:56-59 Accessed 30 January 2013.

9. Fitch J, Coyle E, Gallagher N. Median filtering by threshold decomposition. . *IEEE Transactions on Acoustics, Speech and Signal Processing.* 1984;ASSP—32, No. 6:1183-1188.

10. Saha B, Ray N. Image thresholding by variational minimax optimization. *Pattern Recognition.* 2009;42:843-856.

11. Fang Q, Boas D. Tetrahedral mesh generation from volumetric binary and gray-scale images. *Proceedings of IEEE International Symposium on Biomedical Imaging.* 2009:1142-1145.

12. CGAL, Computational Geometry Algorithms Library. Available at: http://www.cgal.org.

13. The Ennex™ Companies-Advanced Technology Concepts. Available at: http://www.ennex.com/~fabbers/StL.asp.

14. Weissheimer A, Menezes LMD, Sameshima GT, Enciso R, Pham J, Grauer D. Imaging software accuracy for 3-dimensional analysis of the upper airway. *American Journal of Orthodontics and Dentofacial Orthopedics.* 2012;142:801-813.

15. Schendel SA, Hatcher D. Automated 3-dimensional airway analysis from cone-beam computed tomography data. *Journal of Oral and Maxillofacial Surgery.* 2010;68:696-701.

16. Schulze R, Heil U, Groß D, et al. Artefacts in CBCT: A review. *Dentomaxillofacial Radiology.* 2011;40:265-273.

17. Endo M, Tsunoo T, Nakamori N, Yoshida K. Effect of scattered radiation on image noise in cone beam CT. *Med Phys.* 2001;28:469-474.

5.3 Semi-automatic segmentation of the upper airway from Cone beam computed tomography scans Part II: reliability and validity

NA Alsufyani, A Hess, M Noga, N Ray, M Al-Saleh, M Lagravere, PW Major

* Submission: To Be Confirmed

Preface

This project was a collaboration between the Departments of Computing Sciences and Dentistry at the University of Alberta. I was responsible for the concept formation, data collection and analysis, and manuscript composition. From the Computing Sciences, Andy Hess was responsible for the algorithm configuration, previous section, and assisted in data collection and analysis, and manuscript composition. Drs. Al-Saleh and Lagravere (from Dentistry) have assisted in data collection and manuscript composition. Drs. Ray (from Computing Sciences), Major (from Dentistry), and Noga (from Radiology and Diagnostic Imaging) were the supervisory authors and were involved with concept formation and manuscript composition.

This research project, of which this thesis is a part, received research ethics approval from the University of Alberta Research Ethics Board, Project Name "Automatic Segmentation of the Upper Airway using Cone Beam Computed Tomography: A validation study", Pro00021181, March 16, 2011.

5.3 Semi-automatic segmentation of the upper airway from Cone beam computed tomography scans: reliability and validity

Abstract

Objectives: to assess reliability, validity, and time efficiency of semi-automatic segmentation using Segura© software of the nasal and pharyngeal airways, against manual segmentation, using meaningful parameters. **Methods:** Pharyngeal and nasal airways from 10 CBCT image sets were segmented manually and semi-automatically using Segura©. To test intra-and inter-examiner reliability, semi-automatic segmentation was repeated 3 times for one examiner then between 3 examiners, respectively. In addition to volume and surface area, point-based analysis was completed to assess the reconstructed 3D models from manual and Segura© segmentation. The time of both methods of segmentation was also recorded to assess time efficiency. **Results:** the reliability and validity of Segura© were excellent (Intra-class correlation coefficient > 90% for volume and surface area). Part analysis showed small distances between the Segura© and manually segmented 3D models (largest difference did not exceed 4.3 mm). Time of segmentation using Segura© was significantly shorter than that for manual segmentation, 49±11.0 vs. 109±9.4 minutes, $p<0.001$. **Conclusion:** Semi-automatic segmentation of the pharyngeal and nasal airways using Segura© was found reliable, valid, and time efficient. Part analysis was key to explain the differences in upper airway volume and provides meaningful and clinically applicable analysis of 3D changes.

5.3.1 Introduction

Three-dimensional (3D) models of the upper airway segmented from Cone-beam computed tomography (CBCT) images have been used to visualize and analyze treatment efficiency in subjects with snoring and obstructive sleep apnea.[1, 2]

Providing accurate modalities for morpho-functional analysis is essential to improve diagnosis, treatment planning, and to assess treatment outcomes. In order to overcome the difficulties related to the complex morphology of the nasal cavity, the gray level heterogeneity of the airway, and thin bony septae, we proposed a semi-automatic segmentation program, Segura© (developed at University of Alberta), specific to the upper airway in the previous section, Chapter 5.2.

Automatic/semi-automatic segmentation methods have not been adequately tested for accuracy.[2] Validating such methods should be completed, ideally, against manual segmentation of the CBCT images of actual human airways such as the work by El and Palomo.[3] However, most studies tend to validate automatic segmentation methods using phantoms constructed into uniform geometries (e.g. cylinder) or replicating the pharynx.[4-7] Since the shape of the pharyngeal airway is similar to a simple hollow tube, studies that focus only on this part of the airway will likely over-represent the true validity of the evaluated tools. In addition, volumetric measurement was the most popular parameter assessed. This parameter is not specific as it disregards the distribution of the change/difference in airway despite supplementing it with local cross-sectional area measurements. The entire airway model needs to be assessed quantitatively and qualitatively.

The purpose of this study is to assess the reliability, validity, and time efficiency of *Segura*©, against manual segmentation, of the nasal and pharyngeal airway using meaningful parameters.

5.3.2 Methods

This study was approved by the Health Research Ethics Board at the University of Alberta. Ten CBCT image sets of adolescent subjects with "normal" upper airways were randomly and retrospectively selected from the Orthodontic Graduate clinic database at the University of Alberta. The images were acquired by the Classic iCAT CBCT scan (Imaging Sciences International, Hatfield, PA). CBCT protocol used a medium-large field of view (16 cm width x 13 cm height), 120 kVp, 24 mAs, 20 seconds scan time, and 0.3 mm voxel size.

The upper airway region of interest (ROI) included the oro-naso-pharynx, the inferior and middle nasal meatuses and extends from the anterior nasal nares to the level of anterior-inferior point of the body of the third cervical vertebra (C3). The maxillary sinuses, superior nasal meatus, and ethmoid air cells were not included. Each CBCT image set was segmented manually and semi-automatically and the time of both methods of segmentation for each CBCT case (n=10) was recorded in minutes to compare time efficiency.

Manual Segmentation

Using the *Mask tool* in Mimics® software [Mimics 15.0, Materialise NV, Leuven, Belgium], the Principal investigator (PI) manually selected the grey-level threshold on each axial slice for the entire ROI (400-430 slices, 0.3 mm slice thickness, 0 mm inter-slice interval). The grey-threshold of the upper airway roughly ranged from -1000 to -500 depending on the location

of the slice and the quality of the scan. The PI adjusted the mask by erasing or adding to the highlighted airway on each slice. Once the upper airway was defined and edited, a 3D model of the mask was created and saved in an ASCII STL format, Figure 5.3.1.

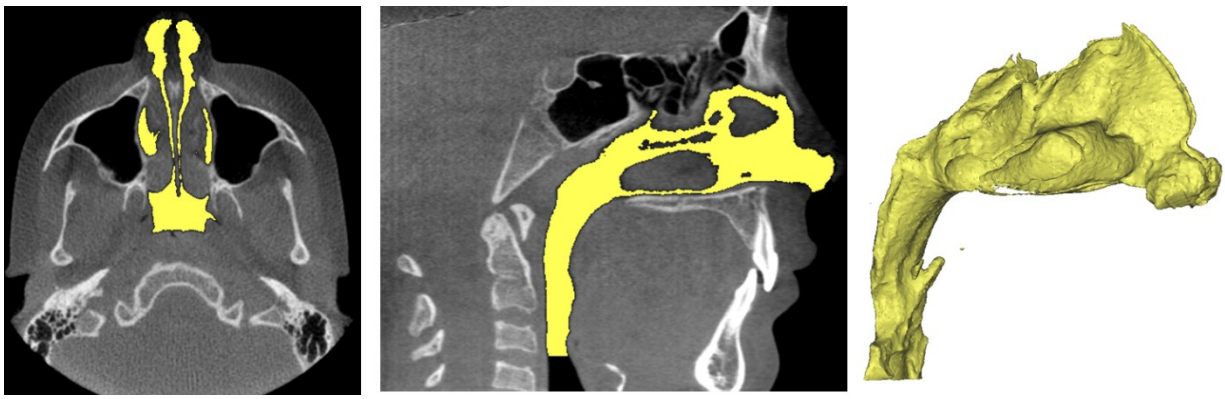


Figure 5.3.1: Manual segmentation. From left to right: Axial CBCT section showing 2D segmentation of the inferior nasal meatus and naso-pharynx, Sagittal CBCT section showing 2D segmentation of the ROI, and Lateral view of the reconstructed 3D model.

Semi-automatic Segmentation

Using *Segura*©, the PI initiated seed-points in the most inferior axial slice in the ROI, i.e. within the oro/hypo-pharyngeal airway, then allowed the seed-points to automatically copy and adjust as the slice moved superiorly towards the nasal cavity within the ROI. The PI would adjust the seed-points, seal unwanted sinuses or airway passages, and edit the boundaries of segmentation when needed, examples of steps used in Segura© are supplemented in Appendix C. Once the upper airway was defined and edited, a 3D model of the segmented ROI was created and saved in an ASCII STL format, Figure 5.3.2.

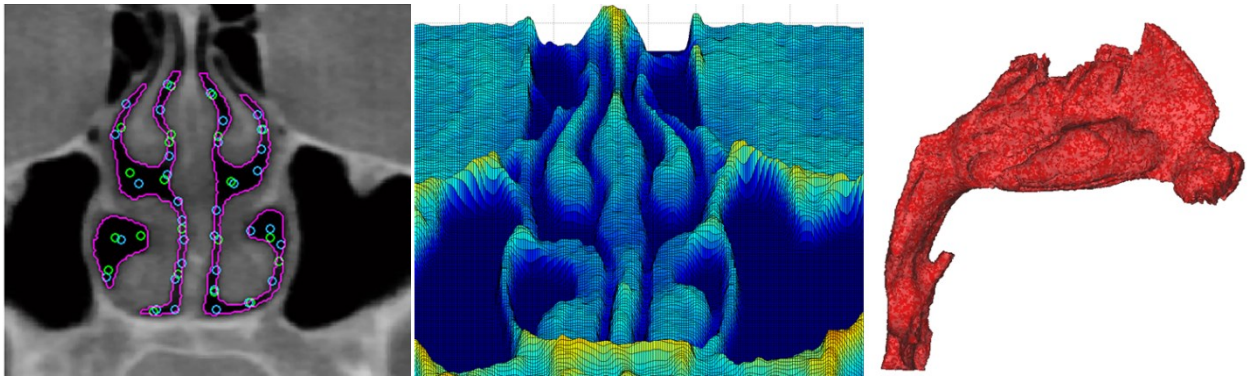


Figure 5.3.2: Semi-automatic segmentation. From left to right: Cropped coronal CBCT section showing the copied seed points with the 2D segmentation of the nasal cavity, 3D histogram of the same image section showing the gradient/depth for segmentation, and Lateral view of the resultant 3D model.

This method of segmentation was completed three times for each CBCT data, by the same PI, one week apart to assess intra-examiner reliability. To test inter-examiner reliability, two additional examiners with experience in CBCT anatomy were familiarized and lightly trained to use *Segura*© using one case not included in the study. Both examiners segmented the same 10 upper airway cases, using the same computer.

3D airway model analysis

3D analysis was performed between the PI's three trials of semi-automatic segmentation using Segura© and between the PI's second trial and the two other examiners to assess intra-and inter-examiner reliability, respectively. To assess validity, 3D analysis was performed between the PI's second trial using Segura© and the PI's manual segmentation. The airway analysis was completed as follows:

The 3D airway models (in .STL format) were exported to 3-matic® [3-matic 7.0, Materialise NV, Leuven, Belgium]. Each model was smoothed by a factor of 0.7 and its surface wrapped. Then, each model pair for comparison was registered using N-point registration followed by global registration in 3-matic®. Point registration allows the PI to manually select

several points (n=10) on the manually segmented model and their match on the semi-auto segmented model, the software then registers both models based on these points. Global registration then fine-tunes the N- point registration.

The total volume and surface area were measured for each airway model. In addition, a point-based analysis using the "*Part comparison analysis"* tool in 3-matic® was applied. This tool was previously used and described by Alsufyani et al[8] (Chapter 4) and measures the distance (in mm) between each triangular node forming the 3D mesh from one airway model to the surfaces of the reference airway model. This comparison was completed between the different models created by intra- and inter-examiner semi-automatic segmentation, then between pairs of semi-automatic and manual segmentation airway models.

Due to the lack of sufficient literature reporting the changes in airway measurements at which clinical significance is noted, the threshold for Part comparison analysis was conservatively set at 2 mm. Triangular node travelling a distance within the threshold boundaries will appear green, a distance < - 2mm will appear blue [minimin part analysis], and a distance > 2mm will appear red [maximum part analysis].

Based on paired T-test for a power of 80%, significance level of 5%, using the volume means and standard deviations between manual and automatic segmentations of the upper airway reported by El and Palomo[3], the sample size average was 14.5 (range 8-21). Power analysis was re-calculated based on the means and standard deviations on the results on our 10 subjects.

Intra-examiner (between the three segmentation trials of Segura©) and inter-examiner reliability (between the three examiners) was tested using the intra-class correlation coefficient

(ICC) of volume and surface area. The mean differences in volume, surface area, and part analyses of the resultant 3D models were assessed with repeated measures ANOVA.

To test validity between the second segmentation of Segura© against that of manual segmentation, the (ICC) of volume and surface area was completed. Also, the difference in volume and surface area of the resultant 3D models was assessed with a paired t-test.

Since the part analysis measures the distances travelled by the triangular nodes from one airway model to the other, only descriptive statistics (mean±standard deviation, minimum, and maximum) are used to report these distances when comparing manual and Segura© segmentations. "Median part analysis" will describe distances traveled within the threshold of -2 and +2mm, whereas "minimum and maximum part analyses" will describe distances traveled beyond + or - 2mm. Small distances show that the compared models are similar in shape, as such the segmentation is reliable and/or valid.

All statistical analyses were completed using IBM SPSS® [IBM SPSS Statistics, V 21.0, Armonk, NY] and significance levels for the paired t-test and repeated measures ANOVA was set at $p < 0.05$.

5.3.3 Results

Despite the intent to exclude superior nasal meatus and ethmoid air cells, there was intra- and inter-examiner variability in segmentation superior extensions. As such, a superior "cutting" plane through the middle nasal meatus was created to limit the superior extent of segmentation. This cutting plane was applied "post-segmentation" on the resultant 3D models of the airways. The superior cutting plane was based on the right and left sphenopalatine foramina posteriorly and a point bisecting the line between the tip of nasal bone and Nasion anteriorly, Figure 5.3.3.

The reliability of landmark identification of sphenopalatine foramina and tip of nasal bone has been verified previously.[8]

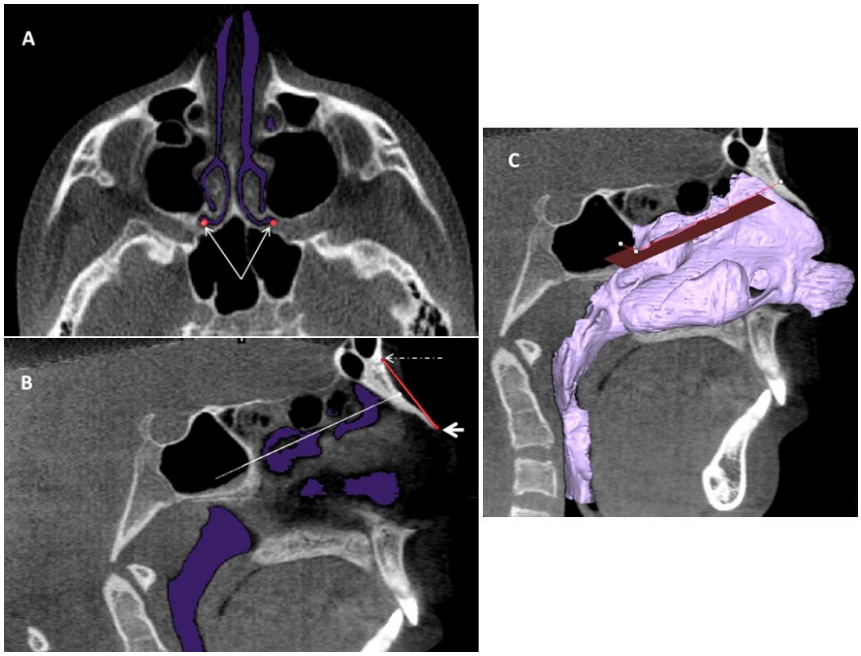


Figure 5.3.3: Superior cutting plane. (A) Cropped axial CBCT section marking right and left sphenopalatine foramina (white arrows), (B) Cropped sagittal CBCT section marking anterior point: middle of bisecting line formed by Nasion (dashed arrow) and tip of nasal bone (arrow head), (C) The resultant superior plane cutting through the upper airway 3D model.

Reliability

The intra-examiner reliability of Segura© segmentation was excellent. The intra-class correlation coefficient (ICC) between the three trials of Segura© was 99.2% (CI 97.8-99.8%) for volume and 99.1% (CI 97.3-99.8%) for surface area. Using the superior cutting plane reduced the differences in volume and surface area and minimally affected part analysis. The average intra-examiner difference in volume and surface area was 2.4±1.3% and 1.2±0.8%, respectively, and in median part analysis was 0.2±0.1 mm. Larger part analysis (distances) ranged between 2.4 and 3.9 mm, table 5.3.1, and were localized, Figure 5.3.4. The differences in minimum part analysis were statistically significant between the second and third trials.

Table 5.3.1: Intra-examiner reliability using Segura©

		Before superior plane definition				After superior plane definition			
Parameters measured		**Mean±SD**	**Minimum**	**Maximum**	**P value**	**Mean±SD**	**Minimum**	**Maximum**	**P value**
Average Volume difference	(cm^3)	1.2 ±1.4	0.2	4.87	NS*	0.6 ±0.3	0.2	1.1	NS*
	(%)	3.6±2.9	1	9		2.4±1.3	1	4.7	
Average Surface area difference	(cm^2)	3.17±2.4	0.3	8.2	NS*	2.6±1.4	0.3	5	NS*
	(%)	1.8±1.4	0.2	4.8		1.2±0.8	0.2	3.1	
Average Mean part analysis (mm)		0.2±0.1	0.0	0.4	NS*	0.2±0.1	0	0.4	NS*
Average Minimum part analysis (mm)		1.6±0.6	0.8	2.7	<0.01^	1.6±0.6	0.8	2.4	<0.01^
Average Maximum part analysis (mm)		3.6±0.6	2.5	4.3	NS*	3.3±0.5	2.5	3.9	NS*
Using Repeated measures ANOVA: *Not significant ^Between 2nd and 3rd trials									

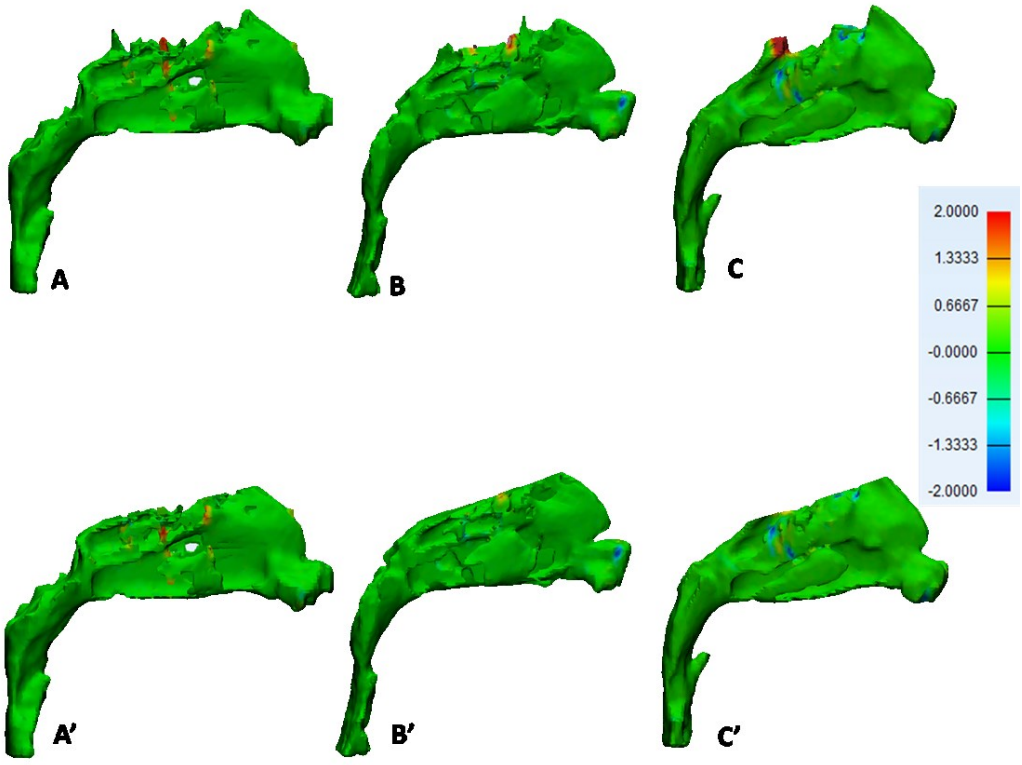


Figure 5.3.4: Examples of larger differences in intra-examiner part analysis. 3D airway models showing part analysis between 2nd and 3rd trials in cases # 8, 9, and 10. A through C without- and A' through C' with superior cutting plane.

Inter-examiner reliability of Segura© segmentation was excellent. The ICC between the three examiners using Segura© was 98.7% (CI 95.6-99.7%) for volume and 97.5% (CI 85-99.4%) for surface area. Using the superior cutting plane largely reduced the differences in surface area and slightly reduced volume and part analysis. The average difference in volume and surface area was 5.5±3.2% and 2.7±1.1%, respectively, and larger differences are noted in subjects 8, 9, and 10, table 5.3.2 and Figure 5.3.5).

Table 5.3.2: Inter-examiner reliability using Segura©

		Before superior cutting plane				After superior cutting plane			
Parameters measured		**Mean±SD**	**Minimum**	**Maximum**	**P value***	**Mean±SD**	**Minimum**	**Maximum**	**P value***
Average Volume difference	(cm^3)	1.8 ±0.6	1	3	<0.05	1.4 ±0.7	0.3	2.7	<0.05^
	(%)	7.4±2.7	3.8	12.5		5.5±3.2	1.2	11.5	
Average Surface area difference	(cm^2)	14.7±4.5	7.7	20.9	≤0.01	4.4±1.9	1.1	8.2	≤0.01^
	(%)	9.6±2.9	4.9	12.9		2.7±1.1	0.7	4.6	
Average Median part analysis (mm)		0.4±0.1	0.0	0.6	NS	0.4±0.1	0.0	0.5	NS
Average Minimum part analysis (mm)		2.4±0.7	1.1	3.5	<0.01^	2.2±0.7	1.1	3.5	<0.01^
Average Maximum part analysis (mm)		4.6±2.6	0.6	9.8	NS	3.5±2.3	0.6	5.8	NS
Time of segmentation process (minutes)	Examiner 1	46.8±6.7	40	60	<0.01				
	Examiner 2	32.3±11.9	18	50					
	Examiner 3	53.5±8.3	38	65					

*Using Repeated measures ANOVA
^Between examiner 2 with examiners 1 and 3

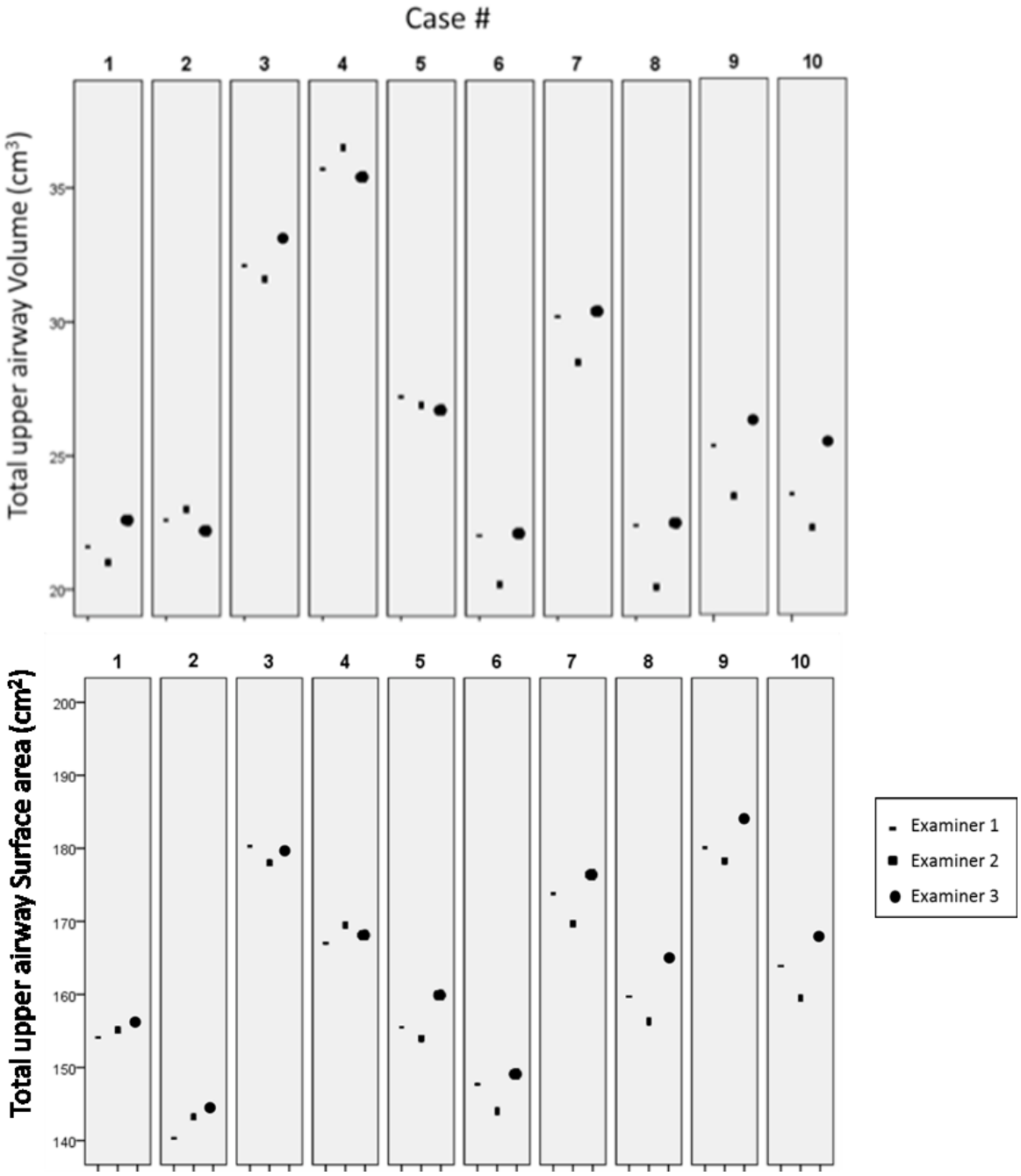


Figure 5.3.5: Box-plots of inter-examiner differences in volume and surface area.

The average difference in median part analysis was 0.4±0.1 mm. Larger part analysis ranged between 3.5 and 5.8 mm, table 5.3.2, and were localized, Figure 5.3.6. In terms of segmentation time, examiner 2 spent the least amount of time (32.3±11.9 minutes) followed by examiner 1 (46.8±6.7 minutes) and examiner 3 (53.5±8.3 minutes). The differences in volume, surface area, and minimum part analysis were statistically significant between the second examiner and the remaining two examiners.

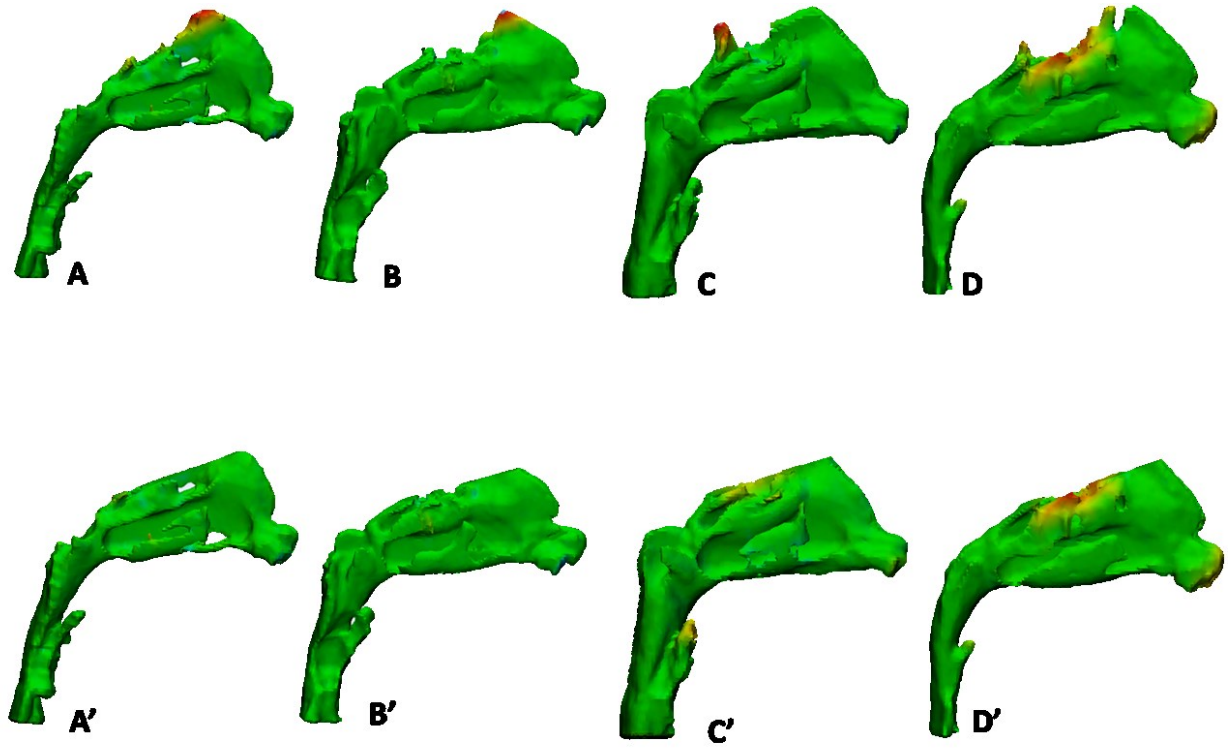


Figure 5.3.6: Examples of larger differences in inter-examiner part analysis. 3D airway models showing part analysis between examiner 2 and 3 in cases # 2, 3, 4, and 10. A through D without- and A' through D' with superior cutting plane.

Validity

The validity of Segura© was excellent. The (ICC) between *Segura*© and manual segmentation was 96.5% (CI 84-99.2%) for volume and 97.2% (CI 89.3-99.3%) for surface area. Using the superior cutting plane reduced the differences in volume and surface area and minimally affected part analysis, table 5.3.3. The difference in volume and surface area was 4.9 ±3.1% and 1.9±0.9%, respectively and the median part analysis was 0.2±0.2 mm. Larger part analyses (distances) ranged between 2.6 and 4.3mm, table 5.3.3, and were localized, Figure 5.3.7.

Time of semi-automatic segmentation using Segura© was statistically significantly shorter than that for manual segmentation, 49±11.01 minutes vs. 109±9.36 minutes, table 5.3.3.

Table 5.3.3: Validity and time efficiency of Segura© against manual segmentation

		Before superior cut plane				After superior cut plane			
Parameters measured		**Mean±SD**	**Minimum**	**Maximum**	**P value**	**Mean±SD**	**Minimum**	**Maximum**	**P value**
Volume difference	(cm^3)	1.9±1.4	0.1	4	NS*	1.2±0.6	0.2	2.4	NS*
	(%)	8.4±7.4	0.4	20.7		4.9±3.1	0.9	11.5	
Surface area difference	(cm^2)	5.4±3.6	0.5	10.6	NS*	3.3±1.7	0.5	6.0	NS*
	(%)	3.2±2.2	0.3	6.9		1.9±0.9	0.3	3.4	
Median part analysis (mm)		0.2±0.2	0.0	0.5	^NA	0.2±0.2	0.0	0.4	^NA
Minimum part analysis (mm)		1.9±0.5	1.3	2.6	^NA	1.8±0.5	1.3	2.6	^NA
Maximum part analysis (mm)		3.8±0.8	2.1	4.6	^NA	3.5±0.6	2.1	4.3	^NA
Time of segmentation process (minutes)	Manual	109±9.4	90	120	<0.001				
	Segura©	49±11.0	40	75					

*Not significant using Paired samples T-test
^Not applicable

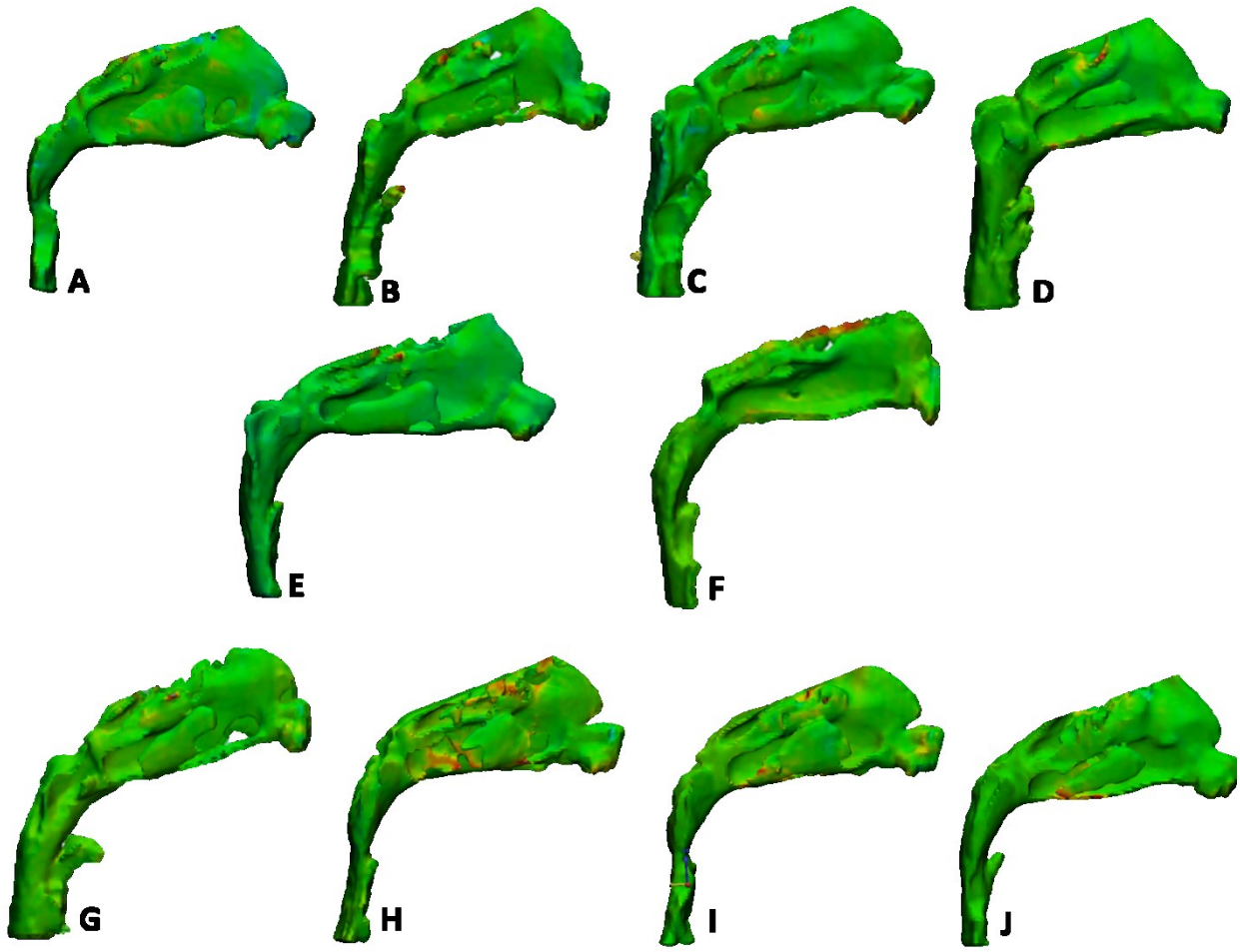


Figure 5.3.7: Part comparison analysis of manual vs. Segura© segmentation. A through J: Lateral views of subjects 1-10, areas in green represent part analysis within the threshold of -2mm to +2 mm, and areas in red or blue represent part analysis > 2mm.

Significant and strong positive correlation was found between median part analysis and differences in surface area as well as volume, table 5.3.4.

Table 5.3.4: Correlation between part analysis and other airway measures

Part comparison analysis	Difference in Surface area	Difference in Volume
Median part analysis	0.76*	0.86**
Minimum part analysis	0.25	0.49
Maximum part analysis	0.12	0.42
*Pearson's correlation is significant at the 0.05 level **Pearson's correlation is significant at the 0.01 level		

Based on our results, power analysis for reliability and validity analyses was 0.99 for volume and surface area and 0.88 for part analysis.

5.3.4 Discussion

Adequate testing of the reliability and accuracy of upper airway 3D models using CBCT-related software is very limited.[2] In order to ascertain the reliability and validity of our previously introduced semi-automatic segmentation program, Segura©, it was necessary to apply this program on both the nasal and pharyngeal airway using meaningful parameters that better explain differences between two objects.

The reliability of Segura© was excellent as shown by the ICC between the three trials of semi-automatic segmentation, 99.2% for volume and 99.1% for surface area. The average mean difference in volume and surface area was small; 0.6±0.3 cm^3 (2.4±1.3%) and 2.6±1.4 cm^2 (1.2±0.8%), respectively, table 5.3.1. El and Palomo[3] tested the reliability of three automatic

segmentation software products for the oropharynx (OP) and the nasopharynx including the inferior nasal meatus (NP), separately, for 30 CBCT image sets. The reliability of the three software tested was higher for OP (ICC 99%) than NP (ICC 88-97%). The mean difference in their volume measurement was a maximum of 0.1 cm^3 for the OP and 0.51 cm^3 for the NP. In this current study we report similar ICC values and slightly higher differences in volume measurements. This may be explained by the fact that we have included more complex anatomy in the nasal cavity which may have introduced larger differences. This is similar to El and Palomo's[3] results where the reliability is higher in the OP than NP due to the "simpler" geometry and ease of segmentation in the OP.

The airway volume is extremely variable, depending on head posture and breathing stage.[3,9-12] Volume and surface area are global, non-specific measures that do not reflect local changes or differences. As such, Part comparison analysis (a point-based analysis) was completed to specify the amount, location and distribution of such differences throughout the entire upper airway. Cevidanes et al [13, 14] used a similar method of analysis to assess 3D surface growth and post-surgical changes in the craniofacial area. The average difference in the median part analysis was very small, 0.2±0.1mm, which is less than the size of one voxel (in this study equals 0.3 mm). Triangular nodes that travelled beyond the distance threshold of 2 mm and -2mm had a mean distance of 3.3±0.5 mm and 1.6±0.6 mm, respectively. Despite the statistical significance between second and third trials in minimum part analysis, the difference did not exceed 2.4 mm. In other words, even when there were local discrepancies between each trial of segmentation, these were not very large (≤3.9mm in either direction) and were mostly localized, Figure 5.3.4.

Inter-examiner reliability of Segura© was excellent; ICC between the three examiners using Segura© was 98.7% for volume and 97.5% for surface area. The average difference in volume and surface area was small; 5.5±3.2% and 2.7±1.1% respectively, as noted in table 5.3.2. Discrepancies between the second examiner with examiner 1 and 3 appear to enlarge in cases 8, 9, and 10, Figure 5.3.5. Of note, mucosal thickening was evident in the nasal cavity of subjects 8, 9, and 10 thus possibly affecting examiner's segmentation and increasing its variability, Figures 5.3.5 and 5.3.6. The average difference in median part analysis was small (0.4±0.1 mm), table 5.3.2, emphasizing high inter-examiner reliability.

Generally, inter-examiner measurement differences are expected to be larger compared to intra-examiner differences. The differences between examiner 2 with examiners 1 and 3 are significant in volume, surface area, and minimum part analysis. Despite the statistical significance, large volume and surface area discrepancies were noted in subjects 8, 9, and 10, Figure 5.3.5. Difference did not exceed 3.5 mm in minimum part analysis and were mostly localized, Figure 5.3.6.

The second examiner spent the least amount of segmentation time, table 5.3.2. The differences between examiners segmentation time ranged between 6.7-21.2 minutes and may reflect the level of experience and familiarity with the upper airway anatomy on CBCT.

The airway model segmented from the second trial was compared to that of manual segmentation to test the validity of Segura©. The (ICC) between Segura© and manual segmentation was excellent, 96.5% for volume and 97.2% for surface area. The difference in volume and surface area was 1.2±0.6 cm^3 (4.9±3.1%) and 3.3±1.7 cm^2 (1.9±0.9%), respectively (table 5.3.3). Considering that these differences are distributed though out the OP and NP airways, the differences in volume are smaller than those reported by El and Palomo[3] ; they

reported volume difference between automatic (3 different programs) and manual segmentation ranging between 0.52 and 2.16 cm^3 for OP and 0.82 and 1.78 cm^3 for NP. Contrary to our results, the distribution or localization of the difference in volume was not elucidated by El and Palomo[3] and were found statistically significant leading the authors to conclude "poor accuracy" and suggest systematic errors of the tested software products. Water et al[15] reported larger differences in volumetric measurement (9-43%) between Dolphin 3D software® and manual segmentation. In their study, the nasal and pharyngeal airways of 20 craniosynostosis subjects were assessed pre- and post- Le fort III osteotomy using CT. The authors concluded that Dolphin 3D software® was not reliable or accurate since the difference in volume, compared to manual segmentation, exceeded the effect of the LFIII osteotomy on airway volume (27%-37%). In our study, Segura© produced models very similar to the ones produce by manual segmentation and larger differences in volume (up to 11.5%) and surface area (up to 3.4%) were, once again, noted in subjects 8, 9, and 10, Figure 5.3.7, arguably due to presence of mucosal thickening of the nasal cavity.

The average difference in part analysis between manual and Segura© segmentation was very small (0.2±0.2 mm), less than the size of one voxel (in this study equals 0.3 mm). Out of thousands of triangular nodes, only 0.1% -1.0% exceeded the distance threshold of 2 mm (3.5±0.6 mm > 2 mm and 1.8±0.5 mm less than -2 mm), table 5.3.3 and Figure 5.3.7. These local discrepancies did not exceed 4.3 mm in either direction and were localized, Figure 5.3.7. Similar to volumetric and surface area findings, part analysis distances larger than 2 mm were noted in airway models of cases 8, 9, and 10 in the nasal cavity Presence of mucosa along with low resolution would hinder the accuracy of the segmentation as it impacts the examiners visualization and the gradient of slide grey-thresholding.[16,17] Albeit, triangular node discrepancies

over 2 mm were localized (< 1% of the entire model) and small (no more than 4.3 mm). To reduce variability in part analysis in the future especially in studies analyzing surgical impacts on the airway, it would be advantageous to divide the upper airway into nasal and pharyngeal parts for analysis and limit the superior extent of segmentation by creating a superior "cutting" plane through the middle nasal meatus based on anatomical landmarks.

An important factor to consider in segmentation is time. Segmentation using Segura© statistically significantly reduced segmentation time by 55% compared to manual segmentation (49±11 minutes vs. 109±9.4 minutes), table 5.3.3. Tingelhoff et al[17] managed to reduce the segmentation time of the nose and paranasal sinuses, using multi-detector CT, by 78.1% however, semi-automatic segmentation of the paranasal sinuses for 3.5 hours was still considered impractical for everyday workflow.[17] In this study, not only was the quantity of time reduced to 49±11 minutes but the quality of time was improved. It was easier to adjust the presence or location of a seed-point within a given 2D slice than to edit (erase or add) the entire boundaries of the grey-threshold selected in manual segmentation. In other words, it is easier for the operator to guide the seed-points to adjust local grey-thresholding than adjusting the resultant global thresholding, within a given 2D slice.

Finally, significant and very strong positive correlation was found between median part analysis and differences in surface area (r=0.76, p=0.01) as well as volume (r=0.86, p=0.001), table 5.3.4. This strongly suggests that the point-based analysis *Part Comparison Analysis* is complementary to the "global" measures of volume and surface area.

Conclusion

Semi-automatic segmentation of the pharyngeal and nasal cavity using Segura© was found reliable, valid, and time efficient. Normal anatomical variations, mucosal thickening or pathology in the nasal cavity may impact the validity and/or time efficiency of the segmentation, however not to severe extents. Using part analysis to assess 3D airway models was key to explain the differences in volume and provides meaningful and clinically applicable analysis of 3D changes.

5.3.5 References

1. Alsufyani NA, Al-Saleh MA, Major PW. CBCT assessment of upper airway changes and treatment outcomes of obstructive sleep apnoea: A systematic review. *Sleep Breath*. 2013;17(3):911-923.

2. Alsufyani NA, Flores-Mir C, Major PW. Three-dimensional segmentation of the upper airway using cone beam CT: A systematic review. *Dentomaxillofacial Radiology*. 2012;41(4):276-284.

3. El H, Palomo JM. Measuring the airway in 3 dimensions: A reliability and accuracy study. *American Journal of Orthodontics and Dentofacial Orthopedics*. 2010;137(4 SUPPL.):S50.e1-S50.e9.

4. Weissheimer A, Menezes LMD, Sameshima GT, Enciso R, Pham J, Grauer D. Imaging software accuracy for 3-dimensional analysis of the upper airway. *American Journal of Orthodontics and Dentofacial Orthopedics*. 2012;142(6):801-813.

5. Ghoneima A, Kula K. Accuracy and reliability of cone-beam computed tomography for airway volume analysis. *Eur J Orthod*. 2013;35(2):256-261.

6. Schendel SA, Hatcher D. Automated 3-dimensional airway analysis from cone-beam computed tomography data. *Journal of Oral and Maxillofacial Surgery*. 2010;68(3):696-701.

7. Alves Jr. M, Baratieri C, Mattos CT, et al. Is the airway volume being correctly analyzed? *American Journal of Orthodontics and Dentofacial Orthopedics*. 2012;141(5):657-661.

8. 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 Medicine, Oral Pathology and Oral Radiology*. 2014;118(3):371-383.

9. Tsuiki S, Almeida FR, Lowe AA, Su J, Fleetham JA. The interaction between changes in upright mandibular position and supine airway size in patients with obstructive sleep apnea. *American Journal of Orthodontics and Dentofacial Orthopedics*. 2005;128(4):504-512.

10. Battagel JM, Johal A, Smith A-, Kotecha B. Postural variation in oropharyngeal dimensions in subjects with sleep disordered breathing: A cephalometric study. *Eur J Orthod*. 2002;24(3):263-276.

11. Dempsey JA, Veasey SC, Morgan BJ, O'Donnell CP. Pathophysiology of sleep apnea. *Physiol Rev*. 2010;90(1):47-112.

12. Trudo FJ, Gefter WB, Welch KC, Gupta KB, Maislin G, Schwab RJ. State-related changes in upper airway caliber and surrounding soft- tissue structures in normal subjects. *American Journal of Respiratory and Critical Care Medicine*. 1998;158(4):1259-1270.

13. Cevidanes LHC, Oliveira AEF, Grauer D, Styner M, Proffit WR. Clinical application of 3D imaging for assessment of treatment outcomes. *Semin Orthod*. 2011;17(1):72-80.

14. Cevidanes LHC, Heymann G, Cornelis MA, DeClerck HJ, Tulloch JFC. Superimposition of 3-dimensional cone-beam computed tomography models of growing patients. *American Journal of Orthodontics and Dentofacial Orthopedics*. 2009;136(1):94-99.

15. de Water VR, Saridin JK, Bouw F, Murawska MM, Koudstaal MJ. Measuring upper airway volume: Accuracy and reliability of dolphin 3D software compared to manual segmentation in craniosynostosis patients. *Journal of Oral and Maxillofacial Surgery*. 2013.

16. Palomo JM, Rao PS, Hans MG. Influence of CBCT exposure conditions on radiation dose. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology*. 2008;105(6):773-782.

17. Tingelhoff K, Moral AI, Kunkel ME, et al. Comparison between manual and semi-automatic segmentation of nasal cavity and paranasal sinuses from CT images. *Annual International Conference of the IEEE Engineering in Medicine and Biology - Proceedings*. 2007:5505-5508.

Chapter 6

Evaluation of anatomic surgical outcomes in children with sleep disordered breathing symptoms using Cone beam CT: A clinical pilot*

NA Alsufyani, M Noga, M Witmans, I Cheng, H El-Hakim, PW Major

*Submission: To Be Confirmed

Preface

This research project, of which this thesis is a part, is an original work by Noura Alsufyani and received research ethics approval from the University of Alberta Research Ethics Board, Project Name "Evaluation of surgical outcomes in children with sleep disordered breathing using Cone Beam computed tomography", Pro00035567, January 24, 2013.

6. Evaluation of anatomic surgical outcomes in children with sleep disordered breathing symptoms using Cone beam CT: A clinical pilot

Abstract

Background: Anatomical obstruction of the upper airway is a common cause to the etiology of paediatric sleep disordered breathing (SDB) and adenoidectomy or tonsillectomy (A or T) is commonly performed in children. Cone beam CT (CBCT) provides insights to the anatomical anomalies found along the upper airway. Prospective studies analyzing the upper airway using CBCT and correlating anatomical airway changes with surgical outcomes in the SDB pediatric population are lacking. **Methods:** 10 children with SDB symptoms and craniofacial disproportions were evaluated by interdisciplinary airway team and underwent (A) or (T). CBCT of the nasal and pharyngeal airways and OSA-18 quality of life questionnaire were completed pre and post-operatively. 3D models of the upper airways were reconstructed, conventional and new airway variables were measured. **Results**: 8 females and 2 males were 8.8±2 years with mean BMI of 18.7±3. OSA-18 improved, median (lower quartile-upper quartile), from 63 (54.7-79.5) to 40 (28.7-43) postoperatively, p=0.007. 3 subjects showed small improvement or worsening in OSA-18 after surgery. The median of all airway measures improved however with very wide range. Subjects with the smallest amounts of constriction relief and gain in airway patency presented with least improvement in OSA-18. New airway measures show strong correlation with changes in OSA-18 (ρ=0.44 and 0.55) whereas conventional measures showed very weak correlation (ρ= -0.04 to 0.37). **Conclusions**: Using point-based analyses, new airway measures were more explanatory than conventional global measures such as volume. Airway patency gained by at least 150% and constriction relief by at least 15% showed marked improvement in OSA-18 by 40-55%, after surgery.

6.1 Introduction

The inter-active roles of adenoid, tonsillar, and nasal turbinates hypertrophy, deviated septum, mouth breathing, and tongue position on orthodontic changes and abnormal craniofacial growth remains ambiguous despite its documentation in the otolaryngology and orthodontic literature.[1-3] Controversies exist regarding the etiology of paediatric sleep disordered breathing (SDB), but most accept smaller airway as the most common cause. Adenotonsillar hypertrophy is considered the most important anatomic cause of such constriction thus prompting the American Academy of Paediatrics recommendation of adenotonisllectomy (AT) as first line of treatment.[4] However, AT is not as effective in treating pediatric obstructive sleep apnea (OSA) as previously thought. High-risk groups and comorbidities were associated with failure rates as high as 54% and information on underlying pathophysiologic mechanisms leading to residual SDB are limited.[5-7] Only one study quantified volumetric changes using MRI in the paediatric upper airway with OSA after AT in which an association between residual adenoid tissue and low success rate of AT by means of polysomnography was found.[7]

Cone beam CT (CBCT) provides insights to the anatomical anomalies found along the upper airway and craniofacial disproportions and has been used to measure anatomic airway changes with surgical and dental appliance treatment for adult SDB/OSA.[8] However, significant drawbacks were related to the questionable accuracy of the reconstructed upper airway 3D models, lack of clinical correlation with CBCT measurements, and the use of global non-specific airway measure such as volume, linear, and cross-sectional area.[8, 9]

Prospective studies analyzing the upper airway, by means of CBCT, and correlating anatomical airway changes with surgical outcomes in the SDB pediatric population are lacking.[8, 10] The aim of this clinical pilot is twofold: to prospectively evaluate anatomical constrictions

and changes that occur in the upper airways before and after AT using 3D airway models from CBCT; and to evaluate whether changes in anatomical airway measures are reflected in the patient's quality of life in a cohort of children and adolescents presenting with jaw disproportions and SDB symptoms.

6.2 Methods

Subjects

Eleven consecutive non-syndromic children-adolescents with SDB symptoms were recruited from the Interdisciplinary Airway Clinic (IARC), Department of Dentistry, University of Alberta. Based on the interdisciplinary evaluation of orthodontist, pediatrician respirologist/sleep medicine specialist, and otolaryngology surgeon, the subjects underwent adenoidectomy (A) and/or tonsillectomy (T). The diagnosis of SDB is based on the history of nocturnal symptoms for at least 12 months, physical examination, overnight pulse oximetry, and Pediatric Sleep Questionnaire (PSQ-22). All subjects completed PSQ-22 and OSA-18 quality of life questionnaires and underwent CBCT imaging, over-night pulse oximetry, and sleep naso-endoscopy at baseline. OSA-18 questionnaire and CBCT imaging were also completed after surgery.

CBCT imaging

The scans were obtained using Next generation iCAT® (Imaging Sciences International, Hatfield, PA) with 0.3 mm voxel, 4 seconds of exposure, 120 kVp, and 5 mA. The field of view extended from the Nasion superiorly to the chin inferiorly, the tip of the nose anteriorly and the

bodies of cervical vertebrae posteriorly. Acquisition of CBCT scans was based on orthodontic reasons where conventional radiography failed to provide adequate information (e.g. maxillary constriction, anteroposterior or vertical jaw discrepancies, asymmetry…). These jaw disproportions are believed to be contributing factors to the SDB symptoms in this cohort with the prospects of maxillary expansion or orthognathic surgeries in their longer treatment plan. The authors do not support the use of CBCT for the sole purpose of airway analysis.

Upper airway analysis

The upper airway region of interest (ROI) included the nasopharynx, oropharynx, and the nasal cavity (inferior and middle nasal meatuses) and extends from the anterior nasal nares to the level of anterior-inferior point of the body of the third cervical vertebra (C3). The ROI was segmented and reconstructed into 3D model (ASCII STL format) using a semi-automatic program developed at the University of Alberta, *Segura*©. Details of Segura©, its reliability, and validity are reported in Chapters 5.2 and 5.3. Using Mimics® [Mimics 15.0, Materialise NV, Leuven, Belgium], pre- and post-surgical CBCT image sets were registered for each subject based on a previously tested method using six anatomical landmarks (Chapter 4).[11] The 3D airway models were then imported and registered onto the "fused" CBCT image volumes using manual translation and rotation followed by global registration which fine-tunes the manual registration. The registered 3D models were exported to 3-matic® [3-matic 7.0, Materialise NV, Leuven, Belgium], smoothed by a factor of 0.7 and its surface wrapped. The upper airway was then divided into nasal cavity (NS), nasopharynx (NP), and oropharynx (OP) for further analysis, Figure 6.1, using three planes. The first plane created by the Posterior nasal spine, right and left

anterior clinoid processes to separate NS from NP. The second plane was created by the mid-anterior-inferior point of the base of odontoid, the right and left anterior-lateral most points of C2 pedicles. The third plane was created by mid-anterior-inferior most point of the body of C3, the posterior-inferior-lateral most points of the body of C3. Details of the three planes provided in Appendix D.

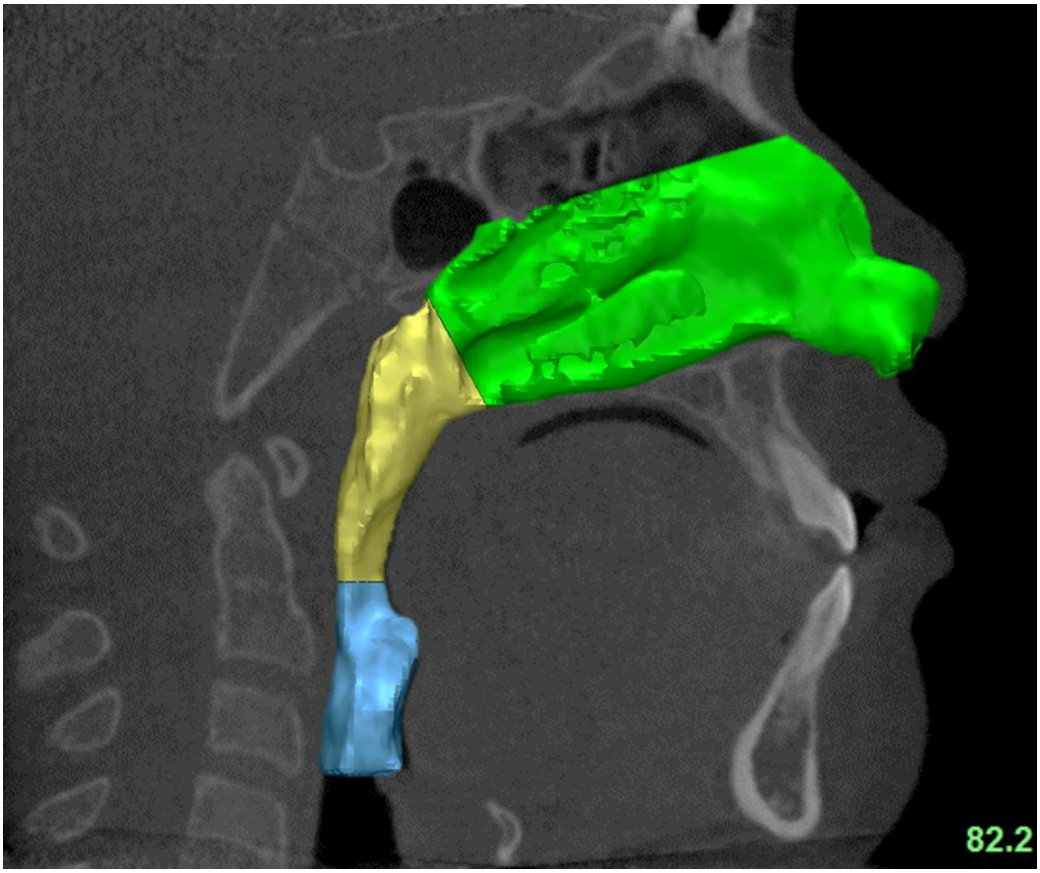


Figure 6.1: Sections of the upper airway. Sagittal CBCT image showing Nose (NS) in green, Nasopharynx (NP) in yellow, and Oropharynx (OP) in blue.

Airway measurements were carried out in 3-matic and consisted of:

1. "Conventional" measures: Volume (cm^3) and surface area (cm^2) of NS, OP, and NP and Minimum cross-sectional area *MinXarea* (mm^2) in OP and NP, at T1 and T2. MinXarea

in OP was identified manually as the smallest medio-lateral dimension on the coronal view, and in the NP as the smallest anterior posterior dimension on the sagittal view, followed by confirmation on the 3D model of the airway.

2. "New" measures: **airway constriction and patency** of each segment at T1 and T2. These represent point-based analysis, referred to as "wall thickness analysis" in 3-matic©, in which the software measures distance of each triangular node forming the 3D mesh of the airway model to the nearest surface based on the normal vector of sampled triangles, Figure 6.2. The total number of triangles forming a model depends on its size and ranges between 20,500 and 40,000. The minimum 3-matic©-system recommendation is Intel Core 2 Duo / AMD X2 AM2 or equivalent, 2 GB RAM, Graphic card with 512 MB RAM, more details in {http://biomedical.materialise.com/3-matic-system-requirements}. The resultant analysis provides minimum, maximum, mean, median, standard deviation, and interquartile range of all the distances from all the triangles. From a given histogram, the percentage of triangles that traveled a distance within a certain threshold set by the operator can be chosen. In this pilot, distances < 0.5 mm in the nasal cavity or <4 mm in the pharyngeal airway represent potential areas of **constriction**. Distances >3mm in nasal cavity or >10 mm in pharyngeal airway were considered areas of **patency**. These cut-off numbers were subjective clinical estimation of expert medical radiologist and maxillofacial radiologist based on the CBCT radiographic appearance of the nasal cavity and pharyngeal airway.
3. Part Comparison analysis of each segment: This tool was previously described by Alsufyani et al[11] and represents point-based analysis to assess the changes in 3D airway models between T1 and T2 to produce a color map. A threshold was set between 4 and

10mm such that areas marked in green represent tissue changes <4mm, orange-yellow represent changes between 4 and 10 mm, and areas marked in red represent changes over 10mm, from T1 to T2.

Conventional and new airway variables are measures before and after surgery, i.e. at T1 and T2, whereas part comparison analysis describes the color map of 3D airway model at T2 subtracted from T1.

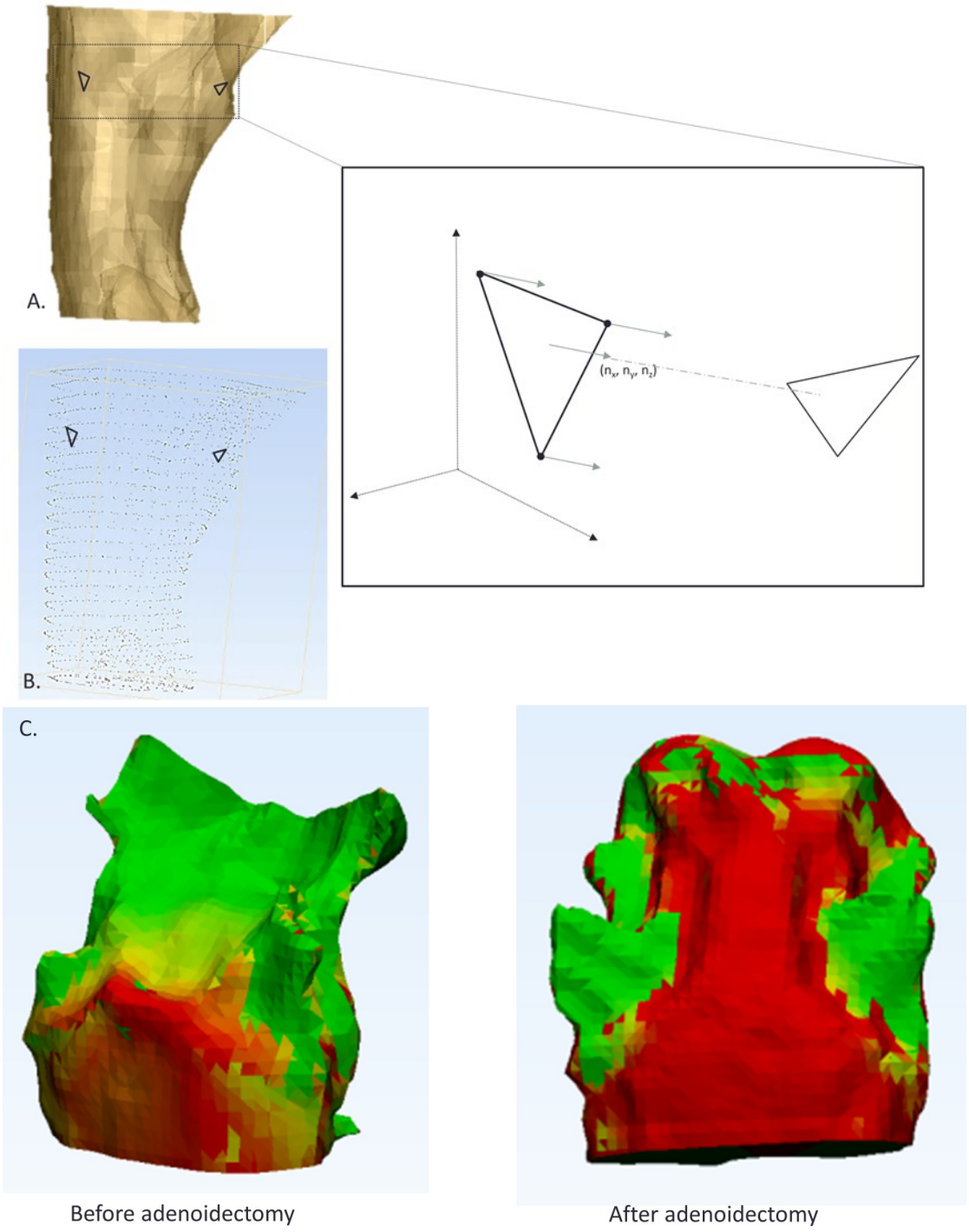


Figure 6.2: New airway measures: airway constriction and patency. (A) 3D model of the oropharynx and (B) triangle nodes forming the model with two sampled triangles: inset shows direction (vector) of one triangle to the nearest triangle on opposing surface. (C) Example of color map where triangles in green represent distances <4mm (i.e. area of constriction at adenoids) and in red > 10 mm (i.e. area of patency increased after adenoidectomy).

Statistical analysis

Statistical analysis was performed using IBM SPSS® [IBM SPSS Statistics 22.0, Armonk, NY]. Means (±standard deviations) are reported for normally distributed variables. For non-parametric variables, median and quartile range marking 25% deviation on each side of the median, much like SD for the mean, are reported as median (lower *Q1*- upper *Q3* quartiles). For paired comparisons between T1 and T2 evaluations, Wilcoxon signed-rank test was used. To assess correlation between new and conventional airway measures and changes in OSA-18, Spearman correlation coefficients were completed. P value < 0.05 was considered significant.

6.3 Results

Eleven subjects were initially included in this pilot however one was excluded due to significant error in neck flexion and tongue positioning impacting the pharyngeal airway where the subject received palatine tonsillectomy. The data of the remaining 10 was not normally distributed with few outliers, except for NS dimensions (was normally distributed). Median (quartile range Q1-Q3) and other non-parametric tests were therefore used in this study, unless specified otherwise.

Demographic/Clinical information

The mean age of the 10 subjects, 8 female and 2 male, was 8.8±2 years. Of the ten, two had allergy and asthma and the mean BMI was 18.7±3 (4 overweight or obese). All subjects present with short anterior cranial base, Sella-Nasion (SN) distance = 60.8±3.1 mm and ranged from 55.5 to 64.9 mm, and five (50%) presented with “long face syndrome”, 3 with narrow maxilla-high arched palate, 2 with skeletal class III. At baseline, all subjects had sleep oximetry

McGill score of 1 (i.e. normal or inconclusive of OSA) and mean PSQ-22 score of 0.50±0.17. Seven (70%) had monopolar suction diathermy adenoidectomy with/without inferior turbinectomy (microdebrider technique) and three (30%) had microdebrider assisted tonsillectomy (2 lingual and 1 palatine) with supraglottoplasty, completed by the same otolaryngologist.

Quality of Life

The median and quartile range for OSA-18 scores at baseline *T1* was 63 (54.7-79.5) and postoperatively *T2* was 40 (28.7-43). The total OSA-18 and sub-domain scores at T1 and T2 are summarized in table 6.1. Subject 9 revealed worsening OSA-18 scores and subjects 6 and 7 presented with the smallest improvements in OSA-18 scores, Figure 6.3.

Table 6.1: Average scores, median (Q1-Q3), for per- and post-operative OSA-18 questionnaires

	T1	T2	Score difference T1-T2		P-value*
			N	%	
Sleep disturbance	17 (12-22)	8 (7.5-10.5)	7.5 (4-10.7)	43.4 (33.3-61)	0.005
Physical suffering	16 (9.5-17.2)	10 (7-11.2)	5 (2.3-6.5)	34.8 (28.1-48)	0.05
Emotional Distress	11.5(8.8-14.3)	7.5 (4-9.5)	3.5 (0.8-6.5)	36.6 (6.2-53.1)	0.03
Daytime problems	9 (6.8-16.5)	5.5 (4-9.7)	2.5 (0.8-7.7)	26.8 (15-47.8)	0.05
Caregiver Concern	14 (8.8-19)	5.5 (4-8.5)	7 (1-11.7)	43.9 (20-71.4)	0.005
Total score	63 (54.7-79.5)	40 (28.7-43)	29 (13.5-38)	43 (31-38)	0.007
*Wilcoxon signed Rank test					

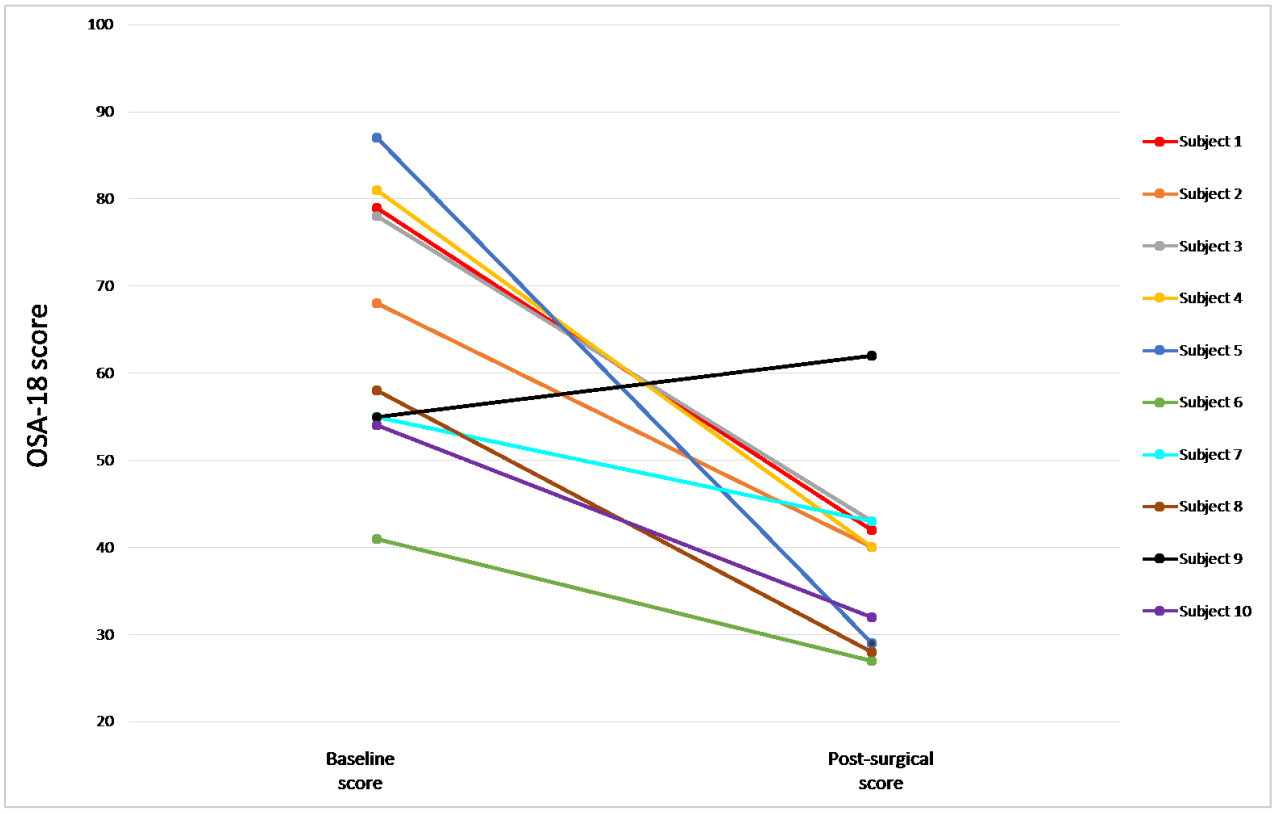
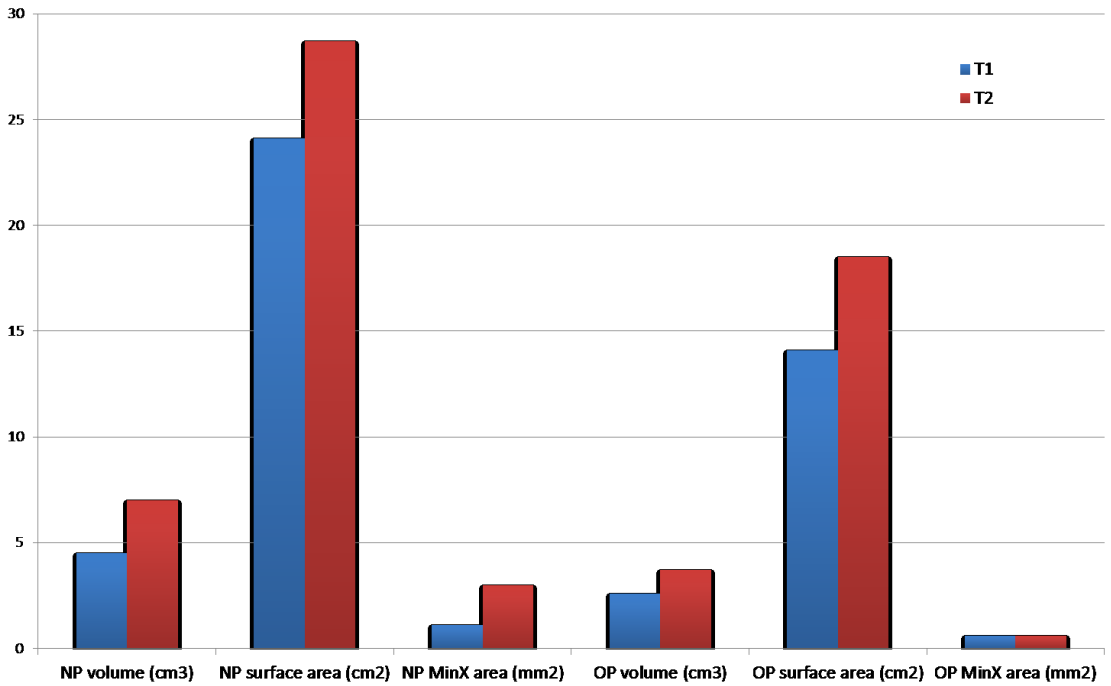


Figure 6.3: Scatter plot of OSA-18 scores before and after surgery per subject.

Airway measurements

None of the subjects presented with significant nasal septum deviations. Generally, changes in NS dimensions from T1 to T2 were not statistically significant using paired t-test: mean volume of the NS was 11.2±3 cm^3 at T1 and 12.1±3.1 cm^3 at T2 (p-value=0.07), mean surface area was 110.8±21.9 cm^2 at T1 and 116.2±3.1 cm^2 at T2 (p-value=0.14), mean nasal airway constriction (i.e. <0.5 mm) was 4.4±1.7% and remained unchanged postoperatively 5±1.8% (p-value= 1), and mean nasal patency (i.e. >3mm) was 16.2±4% at T1 and 18.6±3.9% at T2 (p-value= 0.13). Median "conventional" airway measures, i.e. volume, surface area, and minimum cross-sectional area (MinXarea), for the NP and OP generally increased from T1 to T2 except for MinXarea for the OP that remained unchanged, Figure 6.4.



	NP volume (cm3)	NP surface area (cm2)	NP MinX area (mm2)	OP volume (cm3)	OP surface area (cm2)	OP MinX area (mm2)
T1	4.5 (3.9-6.2)	24.1 (19.6-28.8)	1.1(0.9-1.4)	2.6 (1.8-4.5)	14.1 (11.6-22.8)	0.6 (0.4-1)
T2	7 (5.4-11.3)	28.7 (22.7-36.9)	3 (1.6-3.4)	3.7 (2.2-5.2)	18.5 (13-22.7)	0.6 (0.6-1.6)

Figure 6.4: Bar histogram of "Conventional" upper airway measurements for NP and OP at T1 and T2. Reporting median (quartile range Q1-Q3).

Mean changes in conventional and new airway measures specific to the area of surgery, i.e NP for adenoidectomy and OP for tonsillectomy are presented in table 6.2. Overall, the median of all airway measures in the surgical area showed improvement after surgery however with very wide range.

Table 6.2: Average airway measurements specific to the surgical area

Airway measure	T1	T2	% Score difference T2-T1			P-value*
			Median (Q1-Q3)	Minimum	Maximum	
Volume (cm^3)†	1.1 (0.9-1.4)	3 (1.6-3.4)	37.8 (20-83.6)	4.6	181.8	0.005
Surface area (cm^2) †	2.6 (1.8-4.5)	3.7 (2.2-5.2)	18 (1.3-31.3)	-12.3	70.4	0.04
MinX area (cm^2) †	1 (0.6-1.3)	3 (1.8-3.4)	164.6 (92.1-215.4)	0	433	0.01
Airway constriction <4mm (%)	44 (36.3-53)	28 (23.5-40.8)	24 (11.8-46.1)^	7.7	54	0.005
Airway patency >10mm (%)	3 (1-6)	14 (4.7-24.5)	308 (50-999.5)	-75	1450	0.02

^T1-T2
*Wilcoxon signed rank
† These measures are specific to the area of surgery; NP for adenoidectomy and OP for tonsillectomy

Changes in conventional and new airway variables per subject are presented in Figures 6.5 and 6.6, respectively.

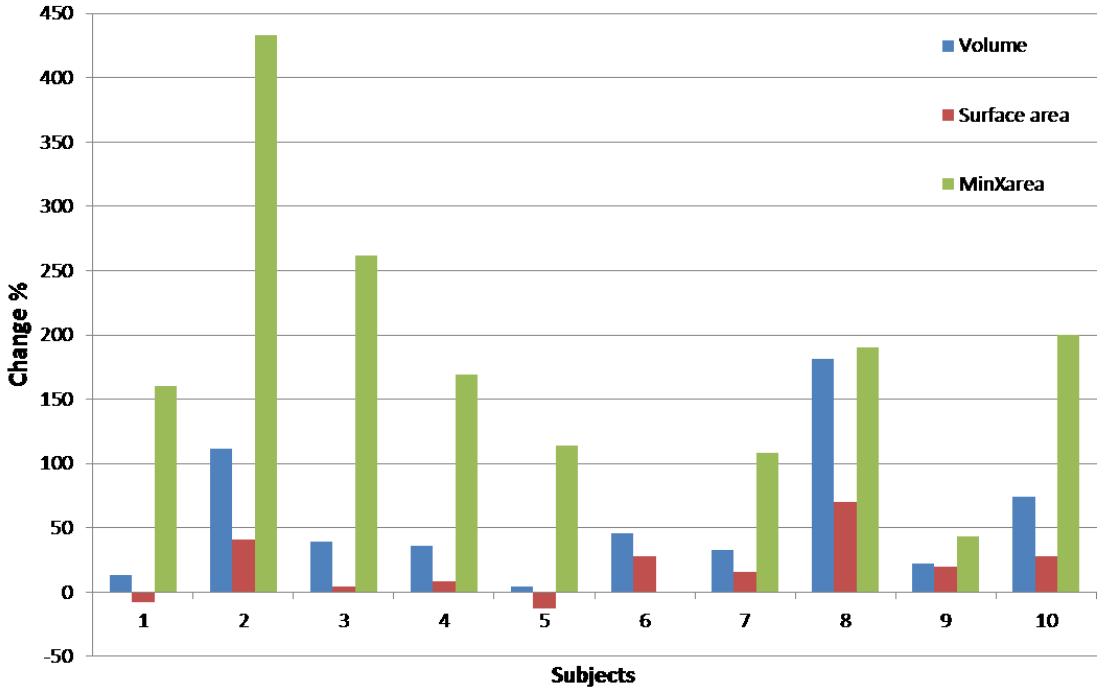


Figure 6.5: Bar Histogram of conventional airway measures specific to surgical area per subject.

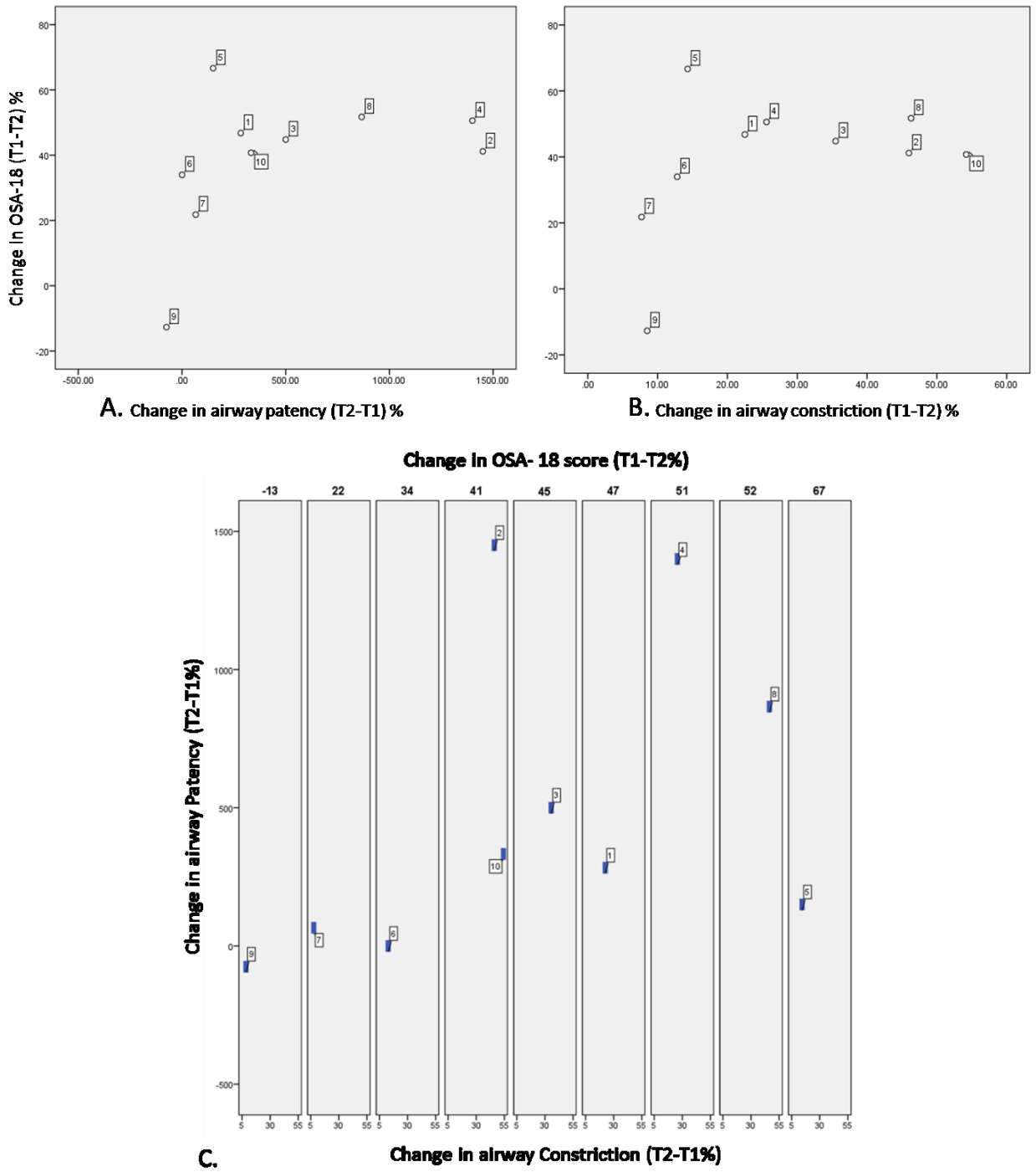


Figure 6.6: Changes in airway patency and constriction vs. quality of life per subject. Individual scatter plots of (A) airway patency and (B) constriction against changes in OSA-18. (C) Multivariable histogram of changes combining airway constriction, patency, and OSA-18 per subject. Subjects 6, 7, and 9 present with the smallest changes in OSA-18, airway constriction (<13%), and patency (< 66%).

Subjects #1 and 5 show reduced surface area and the least improvement in volume, and subject #6 showed no change in MinXarea, Figure 6.5. Using new airway measures, subjects #6, 7, and 9 showed small amounts of constriction relief and gain in patency, Figure 6.6. In fact, subject #9 had lost airway patency after lingual tonsillectomy by 75% and subject #6 had no change in airway patency. Only new airway measures show strong correlation with changes in OSA-18 (ρ=0.44 and 0.55), Figure 6.7.

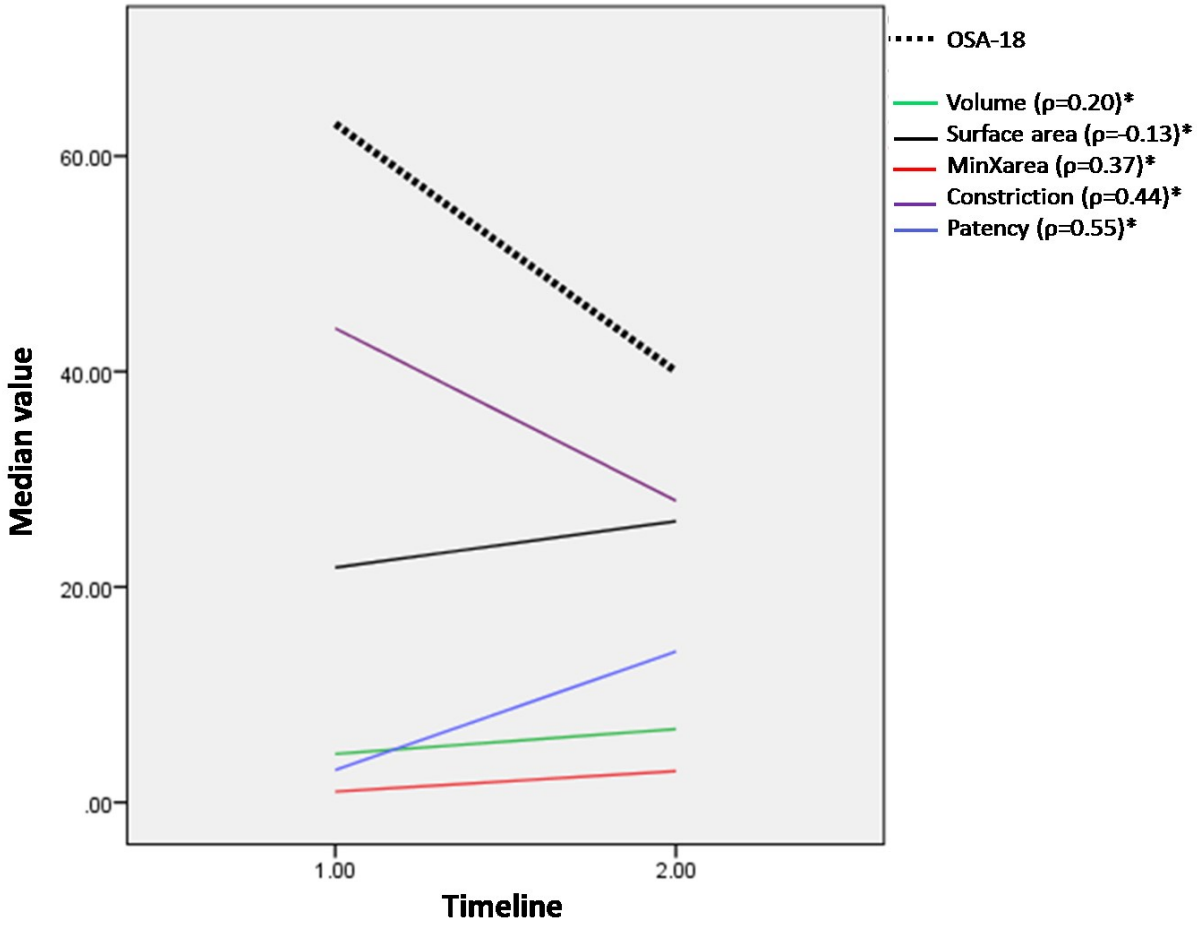


Figure 6.7: Line chart of median airway measures and OSA-18 scores at T and T2. The degree of change from T1 to T2 in the median airway constriction (purple) and patency (blue) is very similar to that of OSA-18, **Spearman-rho =0.44 and 0.55*. Whereas conventional measures show no-weak correlations with OSA-18, **Spearman-rho = -0.13 to 0.37.*

New airway measures shows very strong and significant correlations with conventional measures such as volume and MinXarea, table 6.3.

Table 6.3: Correlation between new and traditional airway measures

	Traditional Measures		
New Measures	**Change in MinXarea (%)**	**Change in Volume (%)**	**Change in surface area (%)**
Relief in Airway constriction %	0.86**	0.69*	0.40
Gain in Airway Patency %	0.88**	0.55	0.24
**Correlation is significant at the 0.01 level (2-tailed). *Correlation is significant at the 0.05 level (2-tailed).			

Part comparison analysis (T2-T1) depicts changes in airway models specific to surgical areas, Figure 6.8. Changes were more noticeable in adenoidectomy cases and least in subjects 6, 7, and 9. Median of tissues gaining space over 4mm was 16.5 % (range 9-46) and for tissues gaining space beyond 10 mm was 1.5% (range 0-7).

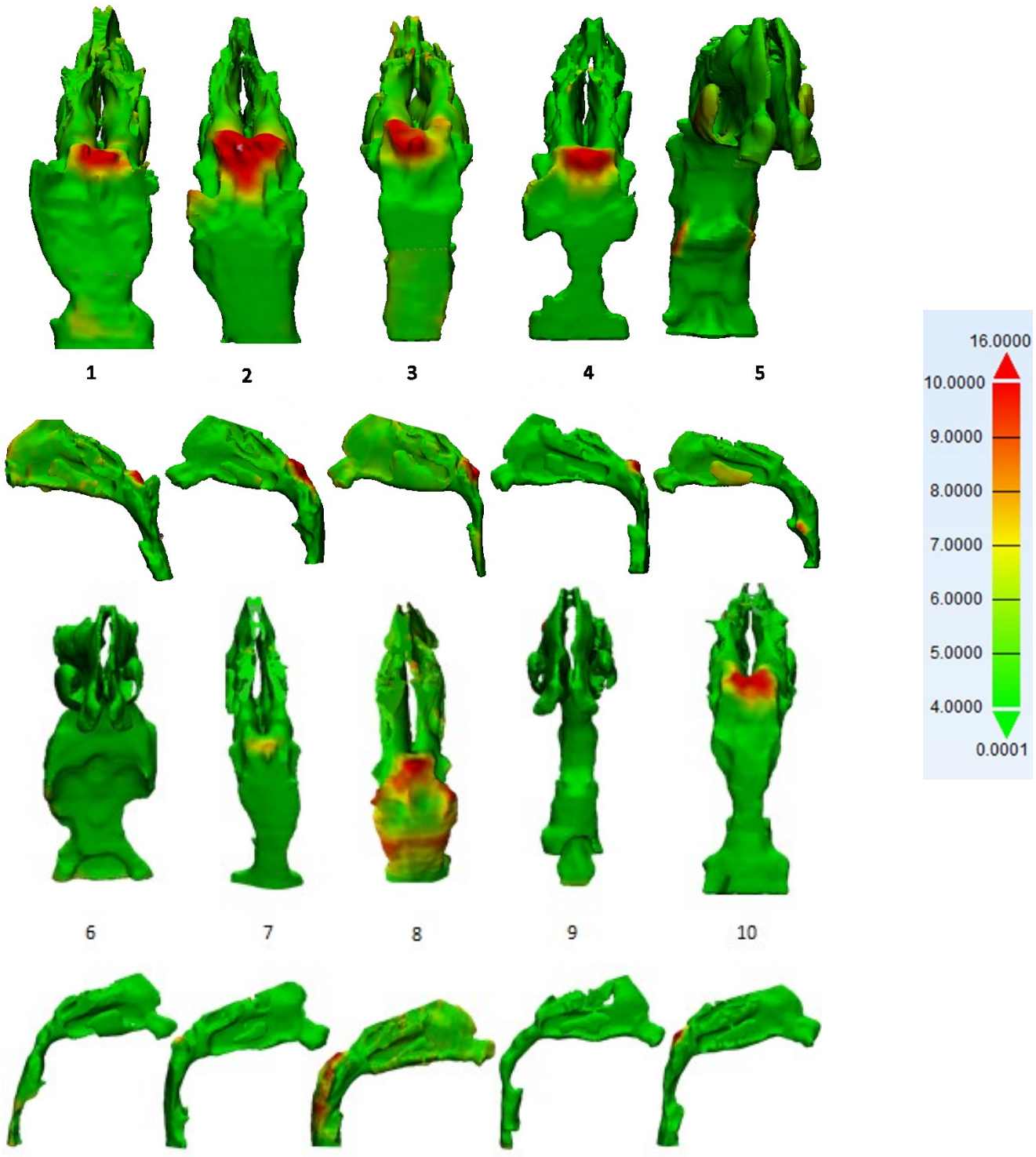


Figure 6.8: Part analysis T2-T1 of subjects 1 though10. Percentage of tissue changes after surgery (>4mm and >10 mm) for subject #1 are (15 and 1), for #2 (26 and 7), for #3 (20 and 2), for #4 (19 and 2), for #5 (9 and 1), for #6 (13 and 0), for #7 (10 and 0), for #8 (46 and 2), for #9 (13 and 0), and for #10 (20 and 2).

6.4 Discussion

SDB in the paediatric population is complex and an interdisciplinary approach from paediatrics, sleep specialists, otolaryngologists, and Orthodontics is recommended.[3] This is to ensure adequate and collaborative diagnosis, treatment planning and outcome assessment. In this level I diagnostic study, we present the use of 3D models of the upper airways reconstructed from CBCT to assess surgical outcomes in 10 children-adolescents presenting with SDB symptoms and jaw disproportions in the interdisciplinary airway clinic.

All 10 subjects (mean age 8.8±2 years) presented with short anterior cranial base, SN= 60.8±3.1 mm, similar to a recent study[12] of OSA children (mean age 9) where mean SN was 61.5±3.4 mm. Compared to normative data published for 10 year olds (mean SN= 63.9±2.6mm[13] and 70.8±2.9mm[14]), children with OSA had shorter cranial base lengths.

Ideally, full polysomnagraphy (PSG) would be used at baseline to diagnose SDB and post-operatively to assess surgical outcome however, it is expensive, time consuming, labor intensive, and limited institutions can use full PSG to diagnose and evaluate pediatric SDB. A validated Pediatric Sleep Questionnaire (PSQ-22) and overnight pulse oximetry can be used as screening tools to identify SDB when PSG is not feasible.[15-17] Although sleep pulse oximetry did not rule out SDB (McGill score= 1) at baseline, the PSQ-22 scores were over the published cut off (≥ 0.33)[15] for 8 subjects out of 10 indicting high risk of pediatric SDB. The surgeries were performed by the same otolaryngolgist and consisted of seven adenoidectomies with/without inferior turbinectomy, two lingual and one palatine tonsillectomies with supraglottoplasty. Turbinectomy reduces the overall size of the nasal turbinates to increase airflow whereas

supraglottoplasty involves the trimming of the floppy supraglottic tissue from the area above the vocal cords found in congenital condition called laryngomalacia.

The aim was to recall subjects by 6 months post-operatively to allow sufficient time for tissues to stabilize and the mean recall period was 7±1.5 months (range 4-9). Overall, the impact of SDB-symptoms on patients' quality of life reduced after surgery in total OSA-18 score and its subdomains, table 6.1. Median total OSA-18 score changed from moderate impact to low, from 63 (54.7-79.5) to 40 (28.7-43). This is based on using the cut off of 60 where total score <60 is low, 60-80 is moderate, and >80 is severe impact on quality of life.[18] Several studies reported changes in OSA-18 in children post AT or tonsillectomy and the mean baseline OSA-18 in these studies ranged from 61.1 to 77.6 and the range of mean postoperative OSA-18 was from 32.5 to 41.[19-22] Compared to these reported numbers, our cohort seems to present with the lower end at T1 and even with subject 9, worsened OSA-18 postoperatively, the median OSA-18 at T2 is still similar to some of the previously reported studies. Subjects 6 and 7 showed the least amount of improvement whereas subject 9 reports worsening of symptoms marked by higher OSA-18 scores in T2 (OSA-18 score was 55 and increased to 62 post-surgically), Figure 6.3. After surgery, the parent of subject 9 reports development of swallowing difficulties, aggressive behavior, and difficulties in waking up in the morning. This is a small sign of the possible neuro-behavioral and reduced neuromuscular tone contributing factors in the realm of pediatric SDB. Of note, subjects 6 and 9 had lingual tonsillectomies and subjects 6 and 7 were siblings with asthma and allergy.

In light of the important role of structural narrowing of the upper airway in the pathogenesis of pediatric SDB, imaging was useful in diagnosing OSA, investigating obstruction sites and airway dynamics in pediatric OSA and their controls.[10] However, only one study

quantified airway changes before and after AT in children with SDB.[7] This pilot is the first to utilize 3D models generated from CBCT to analyze the upper airways pre- and post AT in pediatric SDB.

None of the 10 subjects presented with significant nasal septum deviation and nasal constriction. Nose (NS) volume did not change from T1 to T2 even in the two subjects that underwent turbinoplasty (#7 and 10) possibly due to mucosal thickening/compensation at T2. Generally, median volume and surface area increased from 4.5 to 7 cm^3 and 24.1 to 28.7 cm^2 for NP, and from 2.6 to 3.7 cm^3 and from 14.1 to 18.5 cm^2 for the OP. Median MinXarea increased for NP (from 1.1 to 3 mm^2) but remained the same for OP (0.6 mm^2), Figure 6.4. This is possibly due to false tongue positioning in subject 1 causing significant pseudo-enlargement by 60% of the OP volume at T1, Figure 6.9. Despite fast scanning time (8.9 seconds), proper positioning, and patient instructions to relax the tongue, movement and improper tongue positioning are inevitable in young and active children consequently impacting the shape and dimensions of the oropharyngeal airway.[11] Such errors in neck and tongue posture during the scan would, and should, deem case exclusion from a study if it affects the surgical area.

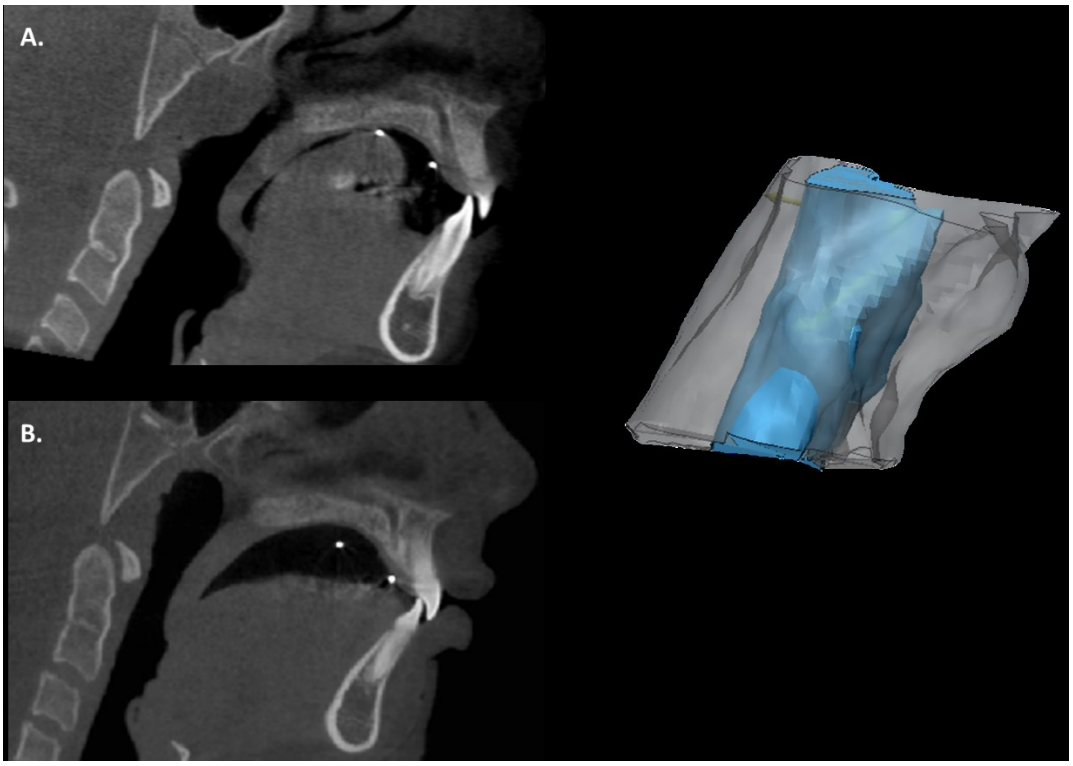


Figure 6.9: Error in tongue position in subject 1. Sagittal CBCT images at baseline (A) with tongue touching the hard palate and postoperatively (B) with tongue resting against anterior teeth. (C) 3D models of the oropharynx at T1 (grey) and T2 (blue) showing pseudo-enlargement of OP at T1 (volume larger by 60%).

Nandalike et al[7] reported similar volume increases in NP (from 2.9±1.3 to 4.4±0.9 cm^3) and in OP (from 3.2±1.2 to 4.3±2.0 cm^3). In their MRI study, 27 obese children with OSA underwent PSG and MRI and the volumes of the NP, OP, adenoids, tonsils, and tongue were measured pre and post AT. In this pilot, conventional and new airway parameters were measured specific to the area of surgery, i.e NP for (A) and OP for (T).

Overall, there was improvement in airway dimensions after surgery however with wide range, table 6.2. Subject 5, showed the smallest increase in volume (by 4%) and subjects 1 and 5 showed reduction in surface area (by 7.7 and 12.3%, respectively), Figure 6.5. Surface area does not necessarily reflect volume since surface area represents the surface boundary forming the

airway whereas the volume represents air inside it thus; a "compressed" pharynx may have large surface area yet contain very small airway volume within it. MinXarea increased for all subjects except for #6; remained unchanged after surgery, Figure 6.5. It was evident that subject 6 had multi-level narrowing in the NP and the adenoidectomy simply removed one of them. This highlights the deficiency in using MinXarea which focuses on one slice and neglects the entire airway.

Using new airway measures, there was relief of constriction by 24% (range 7.7-54) and gain of patency by 308% (range -75 to 1450), table 6.2 and Figure 6.6. In other words, tissues showing airway lumen narrowing <4mm, marking potential sites of collapse, have reduced and areas with over 10 mm patency have increased post-surgically. This however was not the case in subject 9 showing loss of previous patency by 75% and unchanged airway patency in subject 6. Subjects 6, 7, and 9 show the least amounts of changes in airway constriction as well as OSA-18, Figure 6.6. While airway constriction of subject #5 modestly improved by 14.3%, there was a large gain airway patency by 150% after palatine tonsillectomy and presented with the greatest improvement in OSA-18 score by 67%, Figure 6.6. Subjects 6 and 9 underwent lingual tonsillectomy with history of failed AT and thus already present with complexity in which lingual (T) was the last surgical resort. Hypertrophy of the lingual tonsils occurred in one third of children with persistent OSA and along with allergy and asthma present risk factors to residual SDB.[4, 24]

Subject 7 underwent (A) and presented with allergy, asthma, and family history of SDB (i.e. subject 6/sibling) all of which are risk factors to residual SDB.[23, 24]

It appears that gaining airway patency beyond 150% and relieving constriction beyond 15% after surgery did not drastically change scores in the OSA-18; all subjects other than 6, 7,

and 9 tend to “Plateau” at 40-55% improvement in OSA-18 post-surgically, Figure 6.6. This is suggestive of a possible threshold of surgical tissue changes beyond which it has low impact on changes in quality of life. This evidently needs to be verified with a larger sample size.

Changes in all five airway measures were significant after surgery and only new airway parameters showed strong correlation with changes in OSA-18 (Spearman Rho= 0.44 for constriction and 0.55 for patency). There was moderate correlation between changes in OSA-18 and MinXarea (Rho= 0.37) and no-weak correlation with volume and surface area. All correlations were not significant (p-value >0.05) possibly due to the small sample size. This suggests that changes in new airway variables i.e. constriction and patency better represent the degree of changes in OSA-18 compared to conventional measures, Figure 6.7.

Airway constriction and patency showed very strong-strong correlation with the most commonly used airway measures; MinXarea and volume, table 6.3, confirming that point-based analysis is supplemental to global measures however is more explanatory as it takes into account the level(s) of narrowing throughout the entire 3D object i.e. the airway. This is illustrated in Figure 6.8 with the 10 airway models, at T2 subtracted from T1, highlighting the amount and localization of tissues removed and airway space gained. Generally, patients that underwent (A) reveal largest tissue removal except for subject 7. Subject 5 received palatine T, #6 and 9 received lingual (T). Subjects 6, 7, and 9 consistently showed 0% of tissues changing > 10 mm thus show the least amount of tissue removal, Figure 6.8.

Limitations to this pilot need to be addressed. The small sample size, heterogeneity of the surgeries included, and existing outliers severely limit options to statistical tests and hinder the P values reported. Also, point-based analysis in 3-matic© is based on the normal vector of each tringle in the 3D mesh, this can be problematic since the airway geometry is complex and some

tringle vectors will not be perpendicular to the opposing wall and there for can give an "off" distance. This noticed in Figure 6.2C where odd red triangles are noted in a green zone or a green triangle in a red zone. Albeit, the overall average of the analysis should not be affected by these "off" measurements.

Future studies with controls and larger sample size will allow rigorous statistical analyses such as regression and discriminant analyses that ultimately correlate clinical variables and airway measurements at T1 with outcome to provide a prediction model. The search for new and meaningful methods to analyze the morphology of the airway, rather than global measures such as volume and MinXarea, will continue with the possibility of utilizing the 3D airway models in functional analysis to assess air flow.

Conclusions

This pilot is the first to prospectively evaluate anatomical changes in the upper airways after AT using accurate 3D airway models from CBCT with meaningful tools of analysis. In this cohort, it was evident that:

- New airway measures, airway patency and constriction, strongly correlated with quality of life measure (OSA-18) and better explained low scores after surgery in cases 6, 7, and 9.
- Airway patency and constriction also strongly correlated with conventional measures, volume and MinXarea, and proved more explanatory.
- Airway patency gained by at least 150% and constriction relief by at least 15% showed marked improvement in OSA-18 by 40-55%, after surgery.

6.5 References

1. Hatcher DC. Cone beam computed tomography: Craniofacial and airway analysis. *Dent Clin North Am.* 2012;56:343-357.

2. Zettergren-Wijk L, Linder-Aronson S, Nordlander B, Ågren K, Svanborg E. Longitudinal effect on facial growth after tonsillectomy in children with obstructive sleep apnea. *World Journal of Orthodontics.* 2002;3:67-72.

3. Guilleminault C, Li K, Quo S, Inouye RN. A prospective study on the surgical outcomes of children with sleep-disordered breathing. *Sleep.* 2004;27:95-100.

4. Schechter MS. Technical report: Diagnosis and management of childhood obstructive sleep apnea syndrome. *Pediatrics.* 2002;109:e69.

5. Costa DJ, Mitchell R. Adenotonsillectomy for obstructive sleep apnea in obese children: A meta-analysis. *Otolaryngology - Head and Neck Surgery.* 2009;140:455-460.

6. Friedman M, Wilson M, Lin H-, Chang H-. Updated systematic review of tonsillectomy and adenoidectomy for treatment of pediatric obstructive sleep apnea/hypopnea syndrome. *Otolaryngology - Head and Neck Surgery.* 2009;140:800-808.

7. Nandalike K, Shifteh K, Sin S, et al. Adenotonsillectomy in obese children with obstructive sleep apnea syndrome: Magnetic resonance imaging findings and considerations. *Sleep.* 2013;36:841-847.

8. Alsufyani NA, Al-Saleh MA, Major PW. CBCT assessment of upper airway changes and treatment outcomes of obstructive sleep apnoea: A systematic review. *Sleep Breath.* 2013;17:911-923. doi:10.1007/s11325-012-0799-7; 10.1007/s11325-012-0799-7.

9. Alsufyani NA, Flores-Mir C, Major PW. Three-dimensional segmentation of the upper airway using cone beam CT: A systematic review. *Dentomaxillofacial Radiology.* 2012;41:276-284.

10. Slaats MA, Van Hoorenbeeck K, Van Eyck A, et al. Upper airway imaging in pediatric obstructive sleep apnea syndrome. *Sleep Med Rev.* 2014 doi:10.1016/j.smrv.2014.08.001; 10.1016/j.smrv.2014.08.001.

11. 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 Medicine, Oral Pathology and Oral Radiology.* 2014;118:371-383.

12. Korayem MM, Witmans M, MacLean J, et al. Craniofacial morphology in pediatric patients with persistent obstructive sleep apnea with or without positive airway pressure therapy: A cross-sectional cephalometric comparison with controls. *American Journal of Orthodontics and Dentofacial Orthopedics.* 2013;144:78-85.

13. Obloj B, Fudalej P, Dudkiewicz Z. Cephalometric standards for polish 10-year-olds with normal occlusion. *Angle Orthod.* 2008;78:262-269.

14. Thilander B, Persson M, Adolfsson U. Roentgen-cephalometric standards for a swedish population. A longitudinal study between the ages of 5 and 31 years. *Eur J Orthod.* 2005;27:370-389.

15. Chervin RD, Hedger K, Dillon JE, Pituch KJ. Pediatric sleep questionnaire (PSQ): Validity and reliability of scales for sleep-disordered breathing, snoring, sleepiness, and behavioral problems. *Sleep Med.* 2000;1:21-32.

16. Mitchell RB, Garetz S, Moore RH, et al. The use of clinical parameters to predict obstructive sleep apnea syndrome severity in children: The childhood adenotonsillectomy (CHAT) study randomized clinical trial. *JAMA Otolaryngology - Head and Neck Surgery.* 2015;141:130-136.

17. Nixon GM, Kermack AS, Davis GM, Manoukian JJ, Brown KA, Brouillette RT. Planning adenotonsillectomy in children with obstructive sleep apnea: The role of overnight oximetry. *Pediatrics.* 2004;113:e19-25.

18. Franco Jr. RA, Rosenfeld RM, Rao M. Quality of life for children with obstructive sleep apnea. *Otolaryngology - Head and Neck Surgery.* 2000;123:9-16.

19. Kobayashi R, Miyazaki S, Karaki M, et al. Evaluation of adenotonsillectomy and tonsillectomy for pediatric obstructive sleep apnea by rhinomanometry and the OSA-18 questionnaire. *Acta Otolaryngol.* 2014;134:818-823.

20. Lee C-, Kang K-, Weng W-, Lee P-, Hsu W-. Quality of life after adenotonsillectomy in children with obstructive sleep apnea: Short-term and long-term results. *Int J Pediatr Otorhinolaryngol.* 2015;79:210-215.

21. Mitchell RB, Kelly J. Quality of life after adenotonsillectomy for SDB in children. *Otolaryngology - Head and Neck Surgery.* 2005;133:569-572.

22. Ye J, Liu H, Zhang G-, et al. Outcome of adenotonsillectomy for obstructive sleep apnea syndrome in children. *Annals of Otology, Rhinology and Laryngology.* 2010;119:506-513.

23. Bhattacharjee R, Kheirandish-Gozal L, Spruyt K, et al. Adenotonsillectomy outcomes in treatment of obstructive sleep apnea in children: A multicenter retrospective study. *American Journal of Respiratory and Critical Care Medicine.* 2010;182:676-683.

24. Tauman R, Gulliver TE, Krishna J, et al. Persistence of obstructive sleep apnea syndrome in children after adenotonsillectomy. *J Pediatr.* 2006;149:803-808.

Chapter 7

Thesis Conclusion

7.5 General Discussion

7.6 Limitations and Future Directions

7.7 General Conclusions

7.1 General Discussion

The main aim of this dissertation was to assess whether 3D models of the upper airway generated from CBCT can be used as objective tools to assess surgical outcomes in pediatric cohort with SDB symptoms. In **Chapter 2,** the first systematic review revealed that only two studies[1, 2], out of 16, properly tested the reliability of 3D upper airway models generated from CBCT and only one study[1] tested the accuracy of commercial software products against manual segmentation. In the study by El and Palomo[1], they report statistically significant differences between automatic segmentation software products and manual segmentation reaching up to 2163.25 mm^3. Whether this difference is clinically relevant or not cannot be confirmed as volume does not reveal the location or distribution of that change. Furthermore, many studies did not include the nasal cavity. The complex anatomy of the nasal cavity along with the presence of mucous secretions are undoubtedly a hindrance to the ease and accuracy of the segmentation process. None the less, the nasal cavity is an important structure through which the air flows toward the lungs. Any anatomical obstructions in the pharyngeal airway are preceded by nasal obstructions such as nasal septum deviations, bony spurs, concha bullosa, or hypertrophied nasal turbinates. In addition, there were different protocols for airway imaging with no justification for the chosen parameters, and while imaging subjects in the supine position seems to resemble sleeping position, it is far from it. Imaging supine subjects while they are awake is essentially a "snapshot" of their airway and doesn't reflect the dynamics and pharyngeal collapses occurring during the different sleep stages and changes in posture during sleep.[3]

In the second systematic review, the use of CBCT as a tool to assess treatment outcomes on the upper airway found two studies[4, 5], out of seven, that validated airway measures against clinical outcomes. All the studies included were of the OSA-adult population that completed

appliance therapy or maxillary-mandibular advancement (MMA) surgery to increase dimensions of the upper airway. There was a wide range of airway measures selected to assess the change in airway. Particularly, linear and cross-sectional measurements varied greatly and the image section, on which the 2D measurement is chosen, was based on single point of a soft tissue or bone landmarks. In order to create a plane to section the airway, or any object, three points are required to define that plane. In most studies, the authors would select one point (e.g. axial slice at the level of soft palate or hyoid bone) to define the section and rely on patient orientation (x, y, z planes) to complete the plane. This is largely irreproducible.

Collectively, both systematic reviews show that validity and reliability of CBCT-generated 3D models, by means of commercial software, are not clear and the use of global measures such as volume may not truly represent the localised characteristics of the airway geometry. Deficiency in standardized methods to properly section the pharyngeal airway (into naso-, oro-, and hypo-pharynx) or to select areas of interest to measure makes it difficult to compare airway measurements across the different studies. Since most studies were case reports with high risk of bias, high evidence level studies, with statistically appropriate sample sizes, and cross validated clinically are needed. Since the publication of both systematic reviews, several studies utilizing 3D models of the upper airway have emerged. These studies were included in the literature review in **Chapter 1** and one improvement is noted; the studies have shifted from case reports to larger sample sizes. However, the deficiencies are still valid with more studies emerging using volume as their sole outcome measure, using phantoms with very simple geometry to validate a measurement[6], or analyzing changes in the nasal cavity (e.g. after Rapid maxillary expansion) using commercial software products that are based on global thresholding[7-11], and no standards on where to section or measure the airway. Global thresholding refers to the

process of selecting a range of grey threshold values that would represent a tissue of interest. In this thesis, the airway is the area of interest and grey values of air in CBCT are expected to be in the lower range represented by the minus sign next to the grey value (e.g. -700 or -3000). While selecting a range for air in the pharyngeal could work, that range cannot and should not be extended to the nasal cavity. The grey values of air found in the pharynx are not as distinct in the nasal cavity due to volume averaging from surrounding thin bony boundaries or mucous lining of the nose. Bone and mucous will increase the "low" grey values of the nasal airway and thus will not adequately fit into the selected pharyngeal airway threshold. The operator would then have to increase the range of grey threshold to include the nose, at the expense of causing over or under-segmentation in other areas, consider Figure 7.1.1.

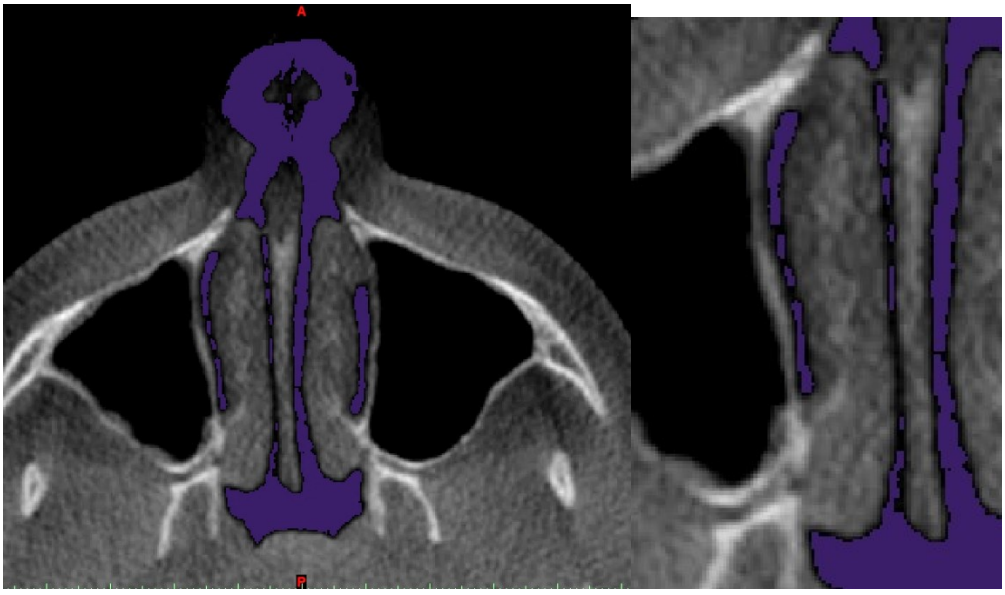


Figure 7.1.1: Axial CBCT image with "global thresholding". The image shows a selected grey value range that perfectly segments the nasopharyngeal airway however "under-segments" in the nasal meatus (close-up image on the right) and "over-segments" the anterior part of the nose. To include all airway passages without impacting the segmentation accuracy of others, it needs to be manually adjusted.

Furthermore, the range of grey-threshold cannot and should not be fixed even for the pharyngeal airway or for specific software such as Dolphin® imaging software (Dolphin Imaging & Management Solutions, Chatsworth, CA) similar to the recent work by Feng et al[12].

This is because grey value of a pixel depends not only on the tissue contrast but also is dependent on other factors such as: type of CBCT machine used, the scanning parameters as it will control the amount of radiation/signal, scattered radiation or metal artifact, patient motion, or machine calibration.[13,14] All factors will cast a change to that pixel value and thus it is unrealistic to standardize an airway threshold.

The need for an accurate segmentation method became clear along with exploring parameters that better analyze the upper airway compared to global measures such as volume. In **Chapter 3**, we attempted to improve the ease of segmentation by testing topical use of radiographic contrast material in the upper airway as they enhance tissue contrast, chapter section 3.1. Despite exploring different methods to deliver barium sulfate and iodine to the nasal cavity, all failed to adequately or uniformly coat the nasal cavity beyond the inferior nasal meatuses. While this might be acceptable for nasal drug delivery, it was not for our purpose. Two factors must be considered in delivering contrast agent to coat the entire upper airway: particle size and flow velocity and this would need to be tested using computational simulation of particle deposition similar to testing drug aerosol. In the next chapter section 3.2, with the collaboration of the Department of Computing Sciences at the University of Alberta, the computational possibility of skeletonization or centerline analysis was tested. Skeletonization represents the "skeleton" of an object and a lot of information can be gained by assessing the distances or curvatures from the center "skeleton" to the periphery "outside boundaries" of an object or the distance from one skeleton to another of two objects. In the skeletonization pilot, we generated the centerlines of two pharyngeal airways using Mimics® then a deformation algorithm was applied to generate "post-surgical tonsillectomy" centerlines. The preliminary results proof the concept of measuring local deformations in the target upper airway region by

measuring the deviations between the centerlines with the possibility of quantifying tolerance threshold beyond which reduced dimensions of the upper airway are not clinically significant. Regrettably, when using paired CBCT data (two CBCT scans of the same subject taken 6 months apart with no surgical intervention) Mimics® software generates drastically different centerlines, Figure 7.1.2. To overcome this, a new algorithm to generate the centerline needs to be developed. This requires extensive computational testing that was not feasible. Accordingly, both pilots in **Chapter 3** were not used in subsequent projects.

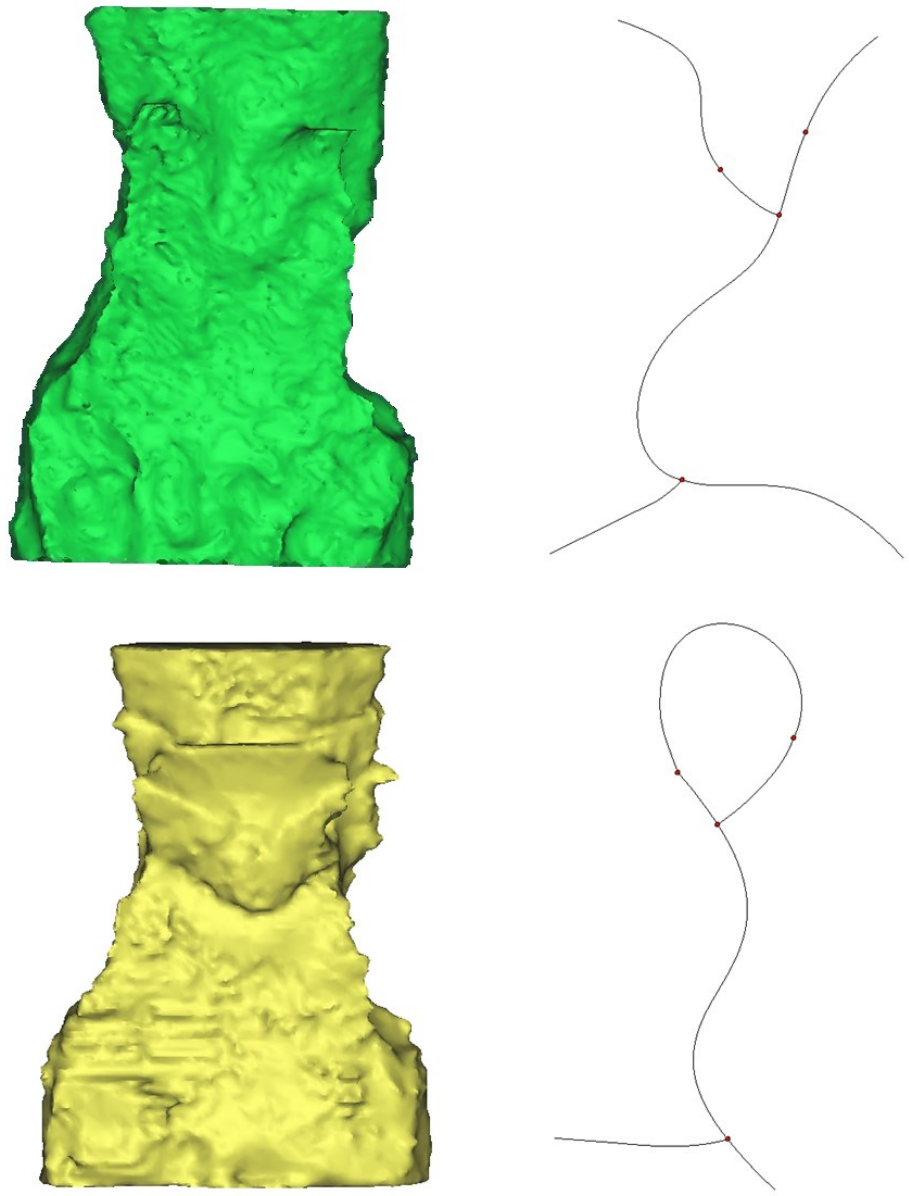


Figure 7.1.2: Errors in centerlines generated by Mimics®. 3D models of the same upper airway at baseline, in green, and 6 months after, in yellow. Note the difference in corresponding centerlines on the right or each model.

With the knowledge that natural head posture changes overtime, it was essential to test a landmark-based registration method specific for airway analysis. In **Chapter 4**, transforming the global coordinate system to a new Cartesian coordinate system using reliable anatomical landmarks was chosen as it provides the option to quantify the change in a given 3D model in the x, y, z axes i.e. expressing magnitude and direction of change in all three axes. For the 22 landmarks, intra- and inter-examiner reliability were high, ICC >98% and 95%, respectively, and mean measurement errors (MEs) were below 1.5 mm. The landmarks tested were distributed in the cranium to select a new coordinate system while others were selected in the vicinity of the upper airway to assess impact of the transformation on the airway. The four most reliable were chosen for the new coordinate system: tip of nasal bone as point of origin, tip of clivus, right and left foramen spinosum. The right and left foramen ovale were used to optimize the transformation as shown by DeCesare et al[15] that 6-point based registration was far more optimum than 4-point based. Changing the coordinate system did not affect MEs (intra-examiner reliability) in fact reduced the overall average distance errors from 1.64 ±0.62 mm in the original image to 1.24±0.37 mm in the transformed image, in single CBCT data i.e. 3T1 data set. In paired CBCT data (T1-T2 data), we introduce another factor in ME i.e. alteration in patient position 6 months apart. Changing the coordinate system reduced T1-T2 MEs to less than 1.5mm (MEs based on original coordinate systems reached up to 7.26 mm). An exception was MEs in the y-axis for C2 (1.78±0.94 mm) and C3 (2.96±1.47 mm). Because the pharyngeal walls are soft tissues formed mainly by muscles and adipose tissue, it is expected to deform in shape due to the displacement pressures from cervical vertebrae (C2 and C3) as the neck flexes. The impact of neck flexion on airway was studied using lateral cephalogram, where 10° change in cranio-cervical inclination (by line through C2 and Sella-Nasion line) or 10 mm change in C3 to

Menton distance, increased the pharyngeal airway space (anteroposterior line from the back of tongue to post pharyngeal wall) by about 4 mm.[16] It was necessary, therefore, to directly assess the ME within the oropharyngeal airway however take into account all aspects of the airway instead of a single airway measurement.

Neck flexion at T1 or T2 scan, in several subjects, caused maximum MEs of 3.09 mm in y axis and 3.75 mm in the z-axis in C2, and 4.66 mm in the y-axis and 4.91 mm in the z-axis in C3. Consequently, this caused apparent discrepancies between T1-T2 pharyngeal airways marked by changes in volume, surface area, and part analysis. After superimposing CBCT T1 and T2 based on the new coordinate system, the mean part analysis was 0.43±0.3 mm and the largest distances travelled by the triangular nodes forming the entire airway model were no more than 5 mm. The largest changes in volume, surface area, and part analysis were found in certain subjects with neck flexion or tongue mal-positioning.

In fact, significant and strong positive correlation was found between C2-C3 inter-landmark distance and the minimum/maximum part analysis distances. In other words, neck flexion producing > 3 mm inter-distance at C2-C3 (in at least one axis) is likely to produce larger distances up to ~5 mm between localized parts of the airway models, overtime. In contrast, there were negligible-weak correlations between C2-C3 distances and airway volume or surface area. Chapter 4 revealed that the described coordinate transformation significantly corrected positioning errors in longitudinal CBCT data, however is unable nor designed to correct for evident neck flexion. Point-based analysis, not volume, was strongly associated with C2-C3 MEs and better explained its impact on airway. Additionally, similar airway discrepancies were found in subjects with significant change in tongue position from T1-T2. This in turn has elucidated the

need to control tongue position and neck flexion in future CBCT airway imaging protocol where surgical treatment of the pharyngeal airway are expected.

Chapter 5 describes the development and testing of a segmentation method that combines the precision and control of manual segmentation and the speed of automatic segmentation. The first chapter section 5.1 reveals a high consistency in manual tracing of 45 sections of the upper airway, traced 3 times per section. This reflects that the PhD student of this thesis has an overall error of < 3 pixels (around 0.9 mm). With this in mind, it was accepted that manual segmentations carried out by the PhD student are acceptable as "the reference" or "truth". In chapter section 5.2, the LEDGES algorithm, *Local Decomposition Gradient Segmentation*, was developed and implemented in a program package named *Segura*© in collaboration with Computing Sciences department at the University of Alberta. The software automatically copies original seeds placed by the operator in the inferior boundary of the pharyngeal airway. The seeds will generate and copy based on the grey threshold and the gradient of the original seeds. In other words, depending of the original grey level selected by the operator, the seeds will find the optimum (i.e. largest) gradient that fits the selected shade of grey. A larger gradient means a sharper boundary and therefore accurate segmentation. This process is done locally within each 2D slice and in sequential slices. The processes allowed assisted manual segmentation in which the software segments automatically but allows user input when and if needed. To test if Segura© was accurate, it had to produce reliable 3D models of 4 simple syringes of known values. Segmenting the 4 syringes five times produced consistent and accurate models that resemble the volumes of the syringes. With regards to time efficiency, the time to segment the upper airway including nasal cavity, paranasal sinuses, and pharyngeal airway using Segura© was compared against that of manual segmentation. Segura© was able to

reduce the segmentation time by 26 (55 minutes vs. 24 hours). Semi-automatic or manual segmentation of the nasal and paranasal airway is seldom in the dental literature however is found in the otolaryngology literature. Fifty five minutes was even shorter than semiautomatic segmentation reported by Tingelhoff et al[17] that took 3.5 hours for detailed segmentation of nasal/paranasal airway.

After ensuring that *Segura*© is precise and consistent in segmenting simple geometry, chapter section 5.3 further tests Segura© using human upper airway based on CBCT scans with detailed analysis of the reconstructed 3D airway models. Using 10 CBCT image sets, the intra- and inter-examiner reliability of 3D airway models produced using Segura© was high (ICC ≥97%) for volume and surface area. The accuracy of Segura© was also high by means of ICC ≥96.5% for volume and surface area against manual segmentation. More importantly, point based analysis using "*part comparison tool*" shows that the mean distances were less than the threshold of 2mm and the largest distances between the airway models did not exceed 3.9 mm, 5.8 mm, and 4.3 mm (for intra-, inter-examiner, and against manual segmentation measurements, respectively), and were very localised.

Despite the intent to exclude superior nasal meatus and ethmoid air cells, there was intra- and inter-examiner variability in segmentation superior extensions marked by red in part comparison analysis color map. As such, a superior cutting plane through the middle nasal meatus was created to standardize the superior extend of segmentation. This generally reduced the differences between the different airway models, however the aforementioned larger and localised differences in airway models were evident in certain cases presenting with mucosal thickening of the nasal cavity indicative of rhinitis, cases 8, 9, and 10. As mentioned previously, the presence of mucous will affect the grey threshold and soft tissue delineation from air. This

can be magnified by different examiners with different expertise, educational background, and comfort in segmenting the nasal cavity.

Segmentation time for Segura© was 49±11.01 minutes vs. 109±9.36 minutes of manual segmentation, p-value <0.001. Not only was the quantity of time reduced but the quality of time was improved. It was easier for the operator to guide the seed-points to adjust local grey-thresholding than adjusting (add/erase) the resultant global thresholding, within a given 2D slice.

Similar to the finding in Chapter 4, significant and very strong positive correlation was found between median part analysis and differences in surface area (r=0.76, p=0.01) as well as volume (r=0.86, p=0.001). This strongly suggests that the point-based analysis *Part Comparison Analysis* is complementary to the "global" measures of volume and surface area. The results indicate that Segura© is reliable, accurate, and time efficient. However, mucosal thickening in the nasal cavity may impact the validity and/or time efficiency of the segmentation, however not to severe extents. Using part analysis to assess 3D airway models was key to explain the differences in volume and provides meaningful and clinically applicable analysis of 3D changes.

Finally, **Chapter 6** includes the implementation of the registration technique described in Chapter 4 along with the semi-automatic segmentation methods in Chapter 5 to analyze the nasal cavity and pharyngeal airways. The clinical pilot recruited 10 children and adolescents with SDB that underwent surgical treatment from the Interdisciplinary airway clinic at the School of Dentistry. This provides a unique advantage to diagnose, treatment plan, and assess treatment progress or outcome from orthodontic, pediatric sleep, and otolaryngology perspectives. Based on the previous chapters, the CBCT scanning protocol was chosen to maximise resolution, reduce radiation dose and reduce scan time to minimize motion. Patients were instructed to bite

on posterior teeth and relax their tongues against their anterior teeth to minimize tongue curling, and radiology technician was instructed to avoid hyper-flexion of the neck. Although 11 children were originally recruited, one presented with significant error in neck flexion and tongue positioning (at baseline where the scan was taken at another institution) thus impacting the pharyngeal airway where the subject received palatine tonsillectomy, Figure 7.1.3 below. Tongue curling was noted in subject 1 (at baseline prior to airway protocol implementation) that affected the oropharynx however not the registration.

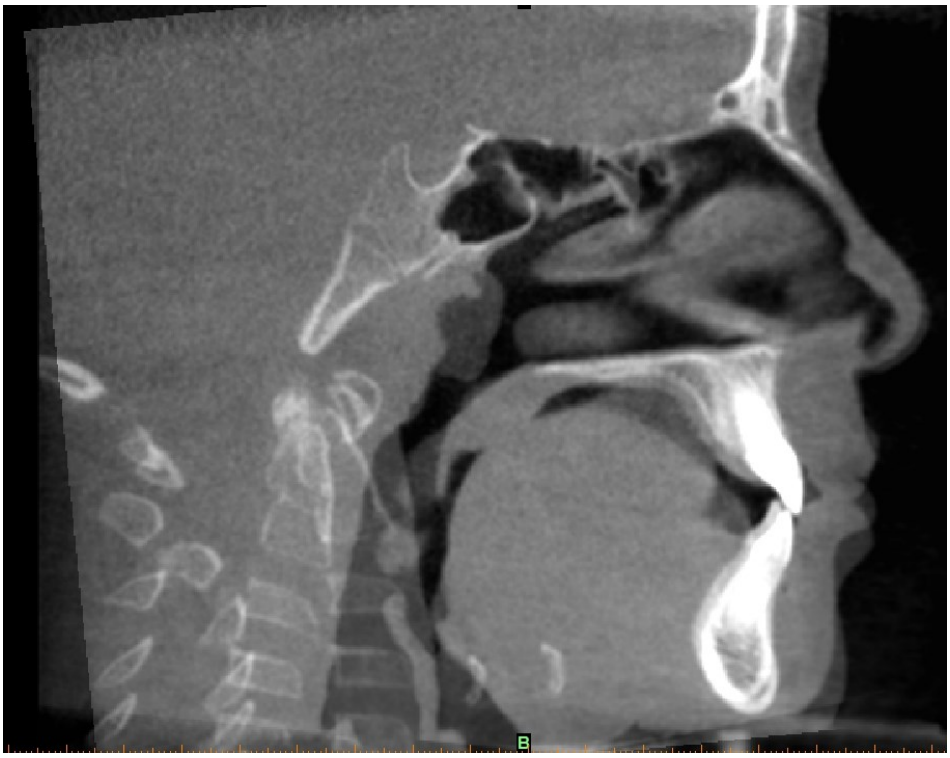


Figure: 7.1.3: Sagittal superimposed CBCT images, T1 and T2, of the excluded case. Note large registration error in neck flexion and perfect registration in the cranial base, nasal cavity, and maxilla.

Based on the PSQ-22, 8 subjects out of 10 presented with high risk of pediatric SDB and the surgeries consisted of seven adenoidectomies, two lingual and one palatine tonsillectomies. The median and quartile range of the total OSA-18 score changed from moderate impact on

quality of life 63 (54.7-79.5) to low impact 40 (28.7-43) after surgery. The least amount of improvement in OSA-18 was found in subjects 6 and 7, and subject 9 reported worsening of symptoms after surgery. While upper airway imaging during wakefulness is unlikely to capture the dynamic interactions between the structures of the upper airway during sleep, it certainly represents the 3D aspect of airway anatomical obstruction. Using 3D airway models, the nasal cavity and pharyngeal airways were analysed by means of conventional and new measures.

The nasal cavity in all 10 subjects did not present with any septal deviations and its dimensions remained unchanged from T1 to T2. The conventional measures (volume, surface area, and minimum cross-sectional area) for the target area (nasopharynx for adenoidectomy and oropharynx for tonsillectomy) generally improved after surgery but with wide ranges and few exceptions. There was only one MRI study in which changes in the upper airway were measured after adenotonsillectomy in obese children.[18] The pharyngeal volume changes in this clinical pilot were similar to the one in the MRI study. Using another point-based analysis tool in Mimics©, named "*wall thickness analysis*", two new airway measures were created. Airway constriction: referring to narrowing of the airway lumen < 4 mm, and airway patency: referring to wide lumen of > 10 mm. After surgery, there was median relief of constriction by 24% (minimum 7.7% and maximum 54%) and gain of patency by 308% (minimum -75% and maximum 1450%). Once again, subject 9 presented loss of previous patency by 75% and unchanged airway patency in subject 6. Subjects 6, 7, and 9 show the least amounts of changes in airway constriction. In other words, subjects 6, 7, and 9 that presented with lowest improvements, or worsened, in OSA-18 showed minimum relief in potential sites of collapse (< 4mm) and minimum gain in patent areas (>10 mm) post-surgically. Only new airway measures reflected the degree of change in OSA-18 by means of strong correlation (ρ=0.44 and 0.55)

compared to conventional measures (ρ=-0.13, 0.20, and 0.37 for surface area, volume, MinXarea, respectively).

Moreover, it appears that gaining airway patency beyond 150% and relieving constriction beyond 15% after surgery did not drastically change scores in the OSA-18; all subjects other than 6, 7, and 9 tend to "Plateau" at 40-55% improvement in OSA-18 post-surgically beyond these two marks. This is suggestive of a possible threshold of surgical tissue changes beyond which it has low impact on changes in quality of life. This evidently needs to be verified with a larger sample size.

Volume and smallest or minimum cross-sectional area are the most common variables used in the literature to assess the upper airway. The new measures, airway patency and constriction, showed very strong correlations with volume and MinXarea ($0.55 \leq r \leq 0.88$). This indicates that new airway measures are complimentary to conventional ones yet they take into account the level(s) of narrowing throughout the entire airway. *Part comparison analysis*, another point-based analysis, conveyed the distribution of the amount of change after surgery, Figure 6.8, by subtracting T2 models from T1. 3D models that received adenoidectomy depicted the largest changes (marked in red) whereas part analyses of subjects 6, 7, and 9 revealed the least tissue changes.

Upper airway measures introduced in this pilot offer a meaningful platform to accurately evaluate anatomical risk factors to postsurgical outcomes using larger cohorts.

7.2 Limitations and Future Directions

- **Chapter 2:** the quality of the studies included on both systematic reviews was low with high risk of bias. Since the publication of both systematic reviews, several studies that fit the inclusion criteria have emerged. Although the literature review in Chapter 1 shows the deficiencies remain, future update of both systematic reviews is recommended.
- **Chapter 3:** the skeletonization pilot was based on two cases, used deformation algorithm to mimic airway surgery, and later the software used did not produce reliable centerlines using longitudinal CBCT data. Future studies can be directed towards developing new algorithms to generate the upper airway centerline, test its reliability using large samples of non-surgical longitudinal CBCT data. Only then can centerline analysis be explored as method to characterize 3D airway models and assess their deformation after surgery.
- **Chapter 4:** the 10 subjects used in the landmark-based registration were 13-17 years old and their CBCT image sets were taken 6 months apart. The performance of the registration technique in younger subjects or longer periods between both scans should be tested in the future. By increasing the sample size and including younger subjects with serial CBCT imaged over 6 months apart, a stronger inference regarding the reliability of landmark-based registration can be reached.
- **Chapter 5:** Although testing of Segura© with conventional measures (volume and surface area) was supplemented by point-based analysis (namely *Part Comparison analysis*), this analysis is based on the normal vector of the triangles creating the 3D model. This potentially is problematic since the complex shape of the airway will place some triangle vectors in a non-perpendicular direction towards the opposing wall. Further testing of Segura© can incorporate the consistency algorithm described in section

5.1 by extending the algorithm into 3D to critically visualize and quantify the segmentation boundaries. In addition, examining the performance of Segura© with different image resolution, multiple examiners with different levels of expertise, and larger samples can be further explored.

- **Chapter 6:** A major limitation is the lack of PSG study to diagnose SDB and assess the surgical outcome in the tested cohort. Also, the patients recruited from the interdisciplinary airway clinic may represent a "special sub-group" of children with SDB symptoms that feature jaw disproportions, referred mainly by dentist/orthodontist suspecting airway problems rather than ones seen at the ENT clinic referred by physicians or pediatricians with serious concerns of sleep, breathing, or with neurocognitive or developmental issues. Due to the small sample size of the pilot, heterogeneity of the surgeries included, and existing outliers the options to statistical testing are limited. Along with concerns regarding normal vector direction in point-based analysis, selecting the MinXarea was subjective/manual and thus may hinder its reproducibility.

  To advance this pilot, larger sample size is required to stratify the sample and apply statistical tests that identify risk factors and create prediction models of surgical outcomes. Airway analysis can be improved by incorporating algorithms in Segura© to automatically calculate cross-sectional area throughout the upper airway, exploration of different thresholds (other than 4mm and 10 mm), further investigation of skeletonization, or applying functional analyses such as computational fluid dynamics (CFD). Using 3D airway models, the airflow can be computationally simulated and assessed post-surgically.

- General limitation is dedicated to the inherent deficiencies of CBCT acquisition of the upper airway. As CBCT is only a "snapshot" of the head, it is an isolated observation of the upper airway and by no means does it dissect the complexity of airway function in the realm of SDB. Also, technical factors defining the image resolution of CBCT, along with the expertise of the operator's segmentation, can vary widely and thus impact the size of the 3D models generated. Finally, despite improving the imaging protocol, children are expected to move, flex their necks, and move their tongues during the scan. Methods to secure head and neck and control tongue position during the scan can be explored. Until then, assessing upper airway changes with tongue or neck mal-position especially in the oropharyngeal airway is not promoted.

7.3 General Conclusions

Within the limitations of this thesis and the results presented, the following can be concluded:

1. The difference in the dimensions of 3D upper airway models generated semi-automatically compared to manual segmentation "the reference" is not clinically relevant. Segura© provides reliable, accurate, and time efficient segmentation of the nasal and pharyngeal airways.
2. Landmark-based registration technique is reliable method for upper airway CBCT superimposition.
3. Point-based analysis (namely *Part Comparison* and *wall thickness analysis*) provides new parameters that take into account localized characteristics of the 3D upper airway, correlated with and complemented conventional/global measures.

4. Using accurate 3D upper airway models, reliable landmark-based registration, and new airway measures (airway patency and constriction) provided objective tools to assess surgical outcome, in pediatric cohort with jaw disproportions and sleep disordered symptoms, when correlated with OSA-18 measures.

7.4 References

1. El H, Palomo JM. Measuring the airway in 3 dimensions: A reliability and accuracy study. *American Journal of Orthodontics and Dentofacial Orthopedics.* 2010;137:S50.e1-S50.e9.

2. Shi H, Scarfe W, Farman A. Upper airway segmentation and dimensions estimation from cone-beam CT image datasets. *Int J CARS.* 2006;1:177-186.

3. Penzel T, Möller M, Becker HF, Knaack L, Peter J-. Effect of sleep position and sleep stage on the collapsibility of the upper airways in patients with sleep apnea. *Sleep.* 2001;24:90-95.

4. El AS, El H, Palomo JM, Baur DA. A 3-dimensional airway analysis of an obstructive sleep apnea surgical correction with cone beam computed tomography. *Journal of Oral and Maxillofacial Surgery.*;In Press, Corrected Proof doi:DOI: 10.1016/j.joms.2010.11.046.

5. Schendel S, Powell N, Jacobson R. Maxillary, mandibular, and chin advancement: Treatment planning based on airway anatomy in obstructive sleep apnea. *Journal of Oral and Maxillofacial Surgery.* 2011;69:663-676.

6. Weissheimer A, Menezes LMD, Sameshima GT, Enciso R, Pham J, Grauer D. Imaging software accuracy for 3-dimensional analysis of the upper airway. *American Journal of Orthodontics and Dentofacial Orthopedics.* 2012;142:801-813.

7. Iwasaki T, Saitoh I, Takemoto Y, et al. Evaluation of upper airway obstruction in class II children with fluid-mechanical simulation. *American Journal of Orthodontics and Dentofacial Orthopedics.* 2011;139:e135-e145.

8. Iwasaki T, Saitoh I, Takemoto Y, et al. Improvement of nasal airway ventilation after rapid maxillary expansion evaluated with computational fluid dynamics. *American Journal of Orthodontics and Dentofacial Orthopedics.* 2012;141:269-278.

9. 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.

10. Smith T, Ghoneima A, Stewart K, et al. Three-dimensional computed tomography analysis of airway volume changes after rapid maxillary expansion. *American Journal of Orthodontics and Dentofacial Orthopedics.* 2012;141:618-626.

11. El H, Palomo JM. Three-dimensional evaluation of upper airway following rapid maxillary expansion A CBCT study. *Angle Orthod.* 2014;84:265-273.

12. Feng X, Li G, Qu Z, Liu L, Näsström K, Shi X-. Comparative analysis of upper airway volume with lateral cephalograms and cone-beam computed tomography. *American Journal of Orthodontics and Dentofacial Orthopedics.* 2015;147:197-204.

13. Schulze R, Heil U, Groß D, et al. Artefacts in CBCT: A review. *Dentomaxillofacial Radiology.* 2011;40:265-273.

14. Endo M, Tsunoo T, Nakamori N, Yoshida K. Effect of scattered radiation on image noise in cone beam CT. *Med Phys.* 2001;28:469-474.

15. DeCesare A, Secanell M, Lagravère MO, Carey J. Multiobjective optimization framework for landmark measurement error correction in three-dimensional cephalometric tomography. *Dentomaxillofacial Radiology.* 2013;42.

16. Muto T, Takeda S, Kanazawa M, Yamazaki A, Fujiwara Y, Mizoguchi I. The effect of head posture on the pharyngeal airway space (PAS). *Int J Oral Maxillofac Surg.* 2002;31:579-583.

17. Tingelhoff K, Moral AI, Kunkel ME, et al. Comparison between manual and semi-automatic segmentation of nasal cavity and paranasal sinuses from CT images. *Annual International Conference of the IEEE Engineering in Medicine and Biology - Proceedings.* 2007:5505-5508 Accessed 30 January 2013.

18. Nandalike K, Shifteh K, Sin S, et al. Adenotonsillectomy in obese children with obstructive sleep apnea syndrome: Magnetic resonance imaging findings and considerations. *Sleep.* 2013;36:841-847.

Bibliography

1. Abdel-Aziz M, Ibrahim N, Ahmed A, El-Hamamsy M, Abdel-Khalik MI, El-Hoshy H. Lingual tonsils hypertrophy; a cause of obstructive sleep apnea in children after adenotonsillectomy: Operative problems and management. *Int J Pediatr Otorhinolaryngol.* 2011;75:1127-1131.
2. Abdullah BJJ, Liam CK, Kaur H, Mathew KM. Parapharyngeal space lipoma causing sleep apnoea. *Br J Radiol.* 1997;70:1063-1065.
3. Abi-Ramia LBP, Carvalho FAR, Coscarelli CT, de Oliveira Almeida MA. Increase in upper airway volume in patients with obstructive sleep apnea using a mandibular advancement device. *Dental Press Journal of Orthodontics.* 2010;15:166-171.
4. 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. *American Journal of Orthodontics and Dentofacial Orthopedics.* 2009;135:468-479.
5. Aboudara CA, Hatcher D, Nielsen IL, Miller A. A three-dimensional evaluation of the upper airway in adolescents. *Orthodontics & craniofacial research.* 2003;6 Suppl 1:173-175.
6. Abramson Z, Susarla S, August M, Troulis M, Kaban L. Three-dimensional computed tomographic analysis of airway anatomy in patients with obstructive sleep apnea. *Journal of Oral and Maxillofacial Surgery.* 2010;68:354-362.
7. Abramson Z, Susarla S, Troulis M, Kaban L. Age-related changes of the upper airway assessed by 3-dimensional computed tomography. *J Craniofac Surg.* 2009;20:657-663.
8. 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. *Journal of Oral and Maxillofacial Surgery.* 2011;69:677-686.
9. Abramson ZR, Susarla S, Tagoni JR, Kaban L. Three-dimensional computed tomographic analysis of airway anatomy. *Journal of Oral and Maxillofacial Surgery.* 2010;68:363-371.
10. Agrama MT. Thyroidectomy for goiter relieves obstructive sleep apnea: Results of 8 cases. *Ear, Nose and Throat Journal.* 2011;90:315-317.
11. Akashiba T, Sasaki I, Kurashina K, Yoshizawa T, Otsuka K, Horie T. Upper airway finding on CT scan with and without nasal CPAP in obstructive sleep apnea patients. *Japanese Journal of Thoracic Diseases.* 1991;29:429-434.
12. Aland Jr. JW. Retropharyngeal lipoma causing symptoms of obstructive sleep apnea. *Otolaryngology - Head and Neck Surgery.* 1996;114:628-630.
13. Alhamad EH, Cosgrove GP. Interstitial lung disease: The initial approach. *Med Clin North Am.* 2011;95:1071-1093.
14. Alobid I, Benítez P, Berenguer J, Bernal-Sprekelsen M, Mullol J. Parapharyngeal angiolipoma causing obstructive sleep apnoea syndrome. *Acta Otolaryngol.* 2004;124:210-212.

15. 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 Medicine, Oral Pathology and Oral Radiology.* 2014;118:371-383.
16. Alsufyani NA, Flores-Mir C, Major PW. Three-dimensional segmentation of the upper airway using cone beam CT: A systematic review. *Dentomaxillofacial Radiology.* 2012;41:276-284.
17. Alves Jr. M, Baratieri C, Mattos CT, et al. Is the airway volume being correctly analyzed? *American Journal of Orthodontics and Dentofacial Orthopedics.* 2012;141:657-661. doi:http://dx.doi.org/10.1016/j.ajodo.2011.11.019.
18. Ando E, Ogawa T, Shigeta Y, et al. A case of obstructive sleep apnoea with anterior cervical osteophytes. *J Oral Rehabil.* 2009;36:776-780.
19. Appelberg J, Janson C, Lindberg E, Pavlenko T, Hedenstierna G. Lung aeration during sleep in patients with obstructive sleep apnoea. *Clinical Physiology and Functional Imaging.* 2010;30:301-307.
20. Arens R, McDonough JM, Corbin AM, et al. Upper airway size analysis by magnetic resonance imaging of children with obstructive sleep apnea syndrome. *American Journal of Respiratory and Critical Care Medicine.* 2003;167:65-70.
21. Arens R, Muzumdar H. Childhood obesity and obstructive sleep apnea syndrome. *J Appl Physiol.* 2010;108:436-444.
22. Armstrong JJ, Leigh MS, Sampson DD, Walsh JH, Hillman DR, Eastwood PR. Quantitative upper airway imaging with anatomic optical coherence tomography. *American Journal of Respiratory and Critical Care Medicine.* 2006;173:226-233.
23. Asakura K, Kataura A. Image diagnosis and function tests--obstructive sleep apnea syndromes. *Nippon Jibiinkoka Gakkai Kaiho.* 1997;100:68-71.
24. Averbeck D. Does scientific evidence support a change from the lnt model for low-dose radiation risk extrapolation? *Health Phys.* 2009;97:493-504.
25. Avrahami E, Englender M. Relation between CT axial cross-sectional area of the oropharynx and obstructive sleep apnea syndrome in adults. *Am J Neuroradiol.* 1995;16:135-140.
26. Avrahami E, Solomonovich A, Englender M. Axial CT measurements of the cross-sectional area of the oropharynx in adults with obstructive sleep apnea syndrome. *Am J Neuroradiol.* 1996;17:1107-1111.
27. Bannink N, Nout E, Wolvius EB, Hoeve HLJ, Joosten KFM, Mathijssen IMJ. Obstructive sleep apnea in children with syndromic craniosynostosis: Long-term respiratory outcome of midface advancement. *Int J Oral Maxillofac Surg.* 2010;39:115-121.
28. Barkdull GC, Kohl CA, Patel M, Davidson TM. Computed tomography imaging of patients with obstructive sleep apnea. *Laryngoscope.* 2008;118:1486-1492.
29. Battagel JM, Johal A, Smith A-, Kotecha B. Postural variation in oropharyngeal dimensions in subjects with sleep disordered breathing: A cephalometric study. *Eur J Orthod.* 2002;24:263-276.

30. Bharadwaj R, Ravikumar A, Krishnaswamy NR. Evaluation of craniofacial morphology in patients with obstructive sleep apnea using lateral cephalometry and dynamic MRI. *Indian Journal of Dental Research.* 2011;22:739-748.
31. Bhattacharjee R, Kheirandish-Gozal L, Spruyt K, et al. Adenotonsillectomy outcomes in treatment of obstructive sleep apnea in children: A multicenter retrospective study. *American Journal of Respiratory and Critical Care Medicine.* 2010;182:676-683.
32. Bhattacharyya N, Blake SP, Fried MP. Assessment of the airway in obstructive sleep apnea syndrome with 3-dimensional airway computed tomography. *Otolaryngology - Head and Neck Surgery.* 2000;123:444-449.
33. Bilston LE, Gandevia SC. Biomechanical properties of the human upper airway and their effect on its behavior during breathing and in obstructive sleep apnea. *J Appl Physiol.* 2014;116:314-324.
34. Bohlman ME, Haponik EF, Smith PL. CT demonstration of pharyngeal narrowing in adult obstructive sleep apnea. *Am J Roentgenol.* 1983;140:543-548.
35. Bolitschek J, Gschwendtner M, Mohr E, Aigner K. Comparative CT-cephalometric and pharyngometric examinations in patients suffering from severe and mild sleep apnoea and in a control group. *Pneumologie.* 1993;47:757-760.
36. Bonilla JA, Pizzuto MP, Brodsky LS. Aplasia of the epiglottis: A rare congenital anomaly. *Ear, Nose and Throat Journal.* 1998;77:51-55.
37. Boulanger P, Flores-Mir C, Ramirez JF, Mesa E, Branch JW. Long term three dimensional tracking of orthodontic patients using registered cone beam CT and photogrammetry. *Conference proceedings : ...Annual International Conference of the IEEE Engineering in Medicine and Biology Society.IEEE Engineering in Medicine and Biology Society.Conference.* 2009;2009:3525-3528.
38. Bowling MR, Cauthen CG, Perry CD, et al. Pulmonary extramedullary hematopoiesis. *J Thorac Imaging.* 2008;23:138-141.
39. Brausewetter F, Hecht M, Pirsig W. Antrochoanal polyp and obstructive sleep apnoea in children. *J Laryngol Otol.* 2004;118:453-458.
40. Brenner DJ, Elliston CD, Hall EJ, Berdon WE. Estimated risks of radiation-induced fatal cancer from pediatric CT. *Am J Roentgenol.* 2001;176:289-296.
41. Brietzke SE, Gallagher D. The effectiveness of tonsillectomy and adenoidectomy in the treatment of pediatric obstructive sleep apnea/hypopnea syndrome: A meta-analysis. *Otolaryngology - Head and Neck Surgery.* 2006;134:979-984.
42. Bruzzi JF, Rémy-Jardin M, Delhaye D, Teisseire A, Khalil C, Rémy J. When, why, and how to examine the heart during thoracic CT: Part 2, clinical applications. *Am J Roentgenol.* 2006;186:333-341.
43. Burger CD, Stanson AW, Daniels BK, Sheedy II PF, Shepard Jr. JW. Fast-computed tomographic evaluation of the effect of route of breathing on upper airway size and function in normal men. *Chest.* 1993;103:1032-1037.

44. Burger CD, Stanson AW, Daniels BK, Sheedy II PF, Shepard Jr. JW. Fast-CT evaluation of the effect of lung volume on upper airway size and function in normal men. *Am Rev Respir Dis.* 1992;146:335-339.
45. Burger CD, Stanson AW, Sheedy II PF, Daniels BK, Shepard Jr. JW. Fast-computed tomography evaluation of age-related changes in upper airway structure and function in normal men. *Am Rev Respir Dis.* 1992;145:846-852.
46. Caballero P, Alvarez-Sala R, García-Río F, et al. CT in the evaluation of the upper airway in healthy subjects and in patients with obstructive sleep apnea syndrome. *Chest.* 1998;113:111-116.
47. Çağlayan F, Tozoğlu U. Incidental findings in the maxillofacial region detected by cone beam CT. *Diagnostic and Interventional Radiology.* 2012;18:159-163.
48. Cahali MB, Formigoni GGS, Gebrim EMMS, Miziara ID. Lateral pharyngoplasty versus uvulopalatopharyngoplasty: A clinical, polysomnographic and computed tomography measurement comparison. *Sleep.* 2004;27:942-950.
49. Capdevila OS, Kheirandish-Gozal L, Dayyat E, Gozal D. Pediatric obstructive sleep apnea: Complications, management, and long-term outcomes. *Proceedings of the American Thoracic Society.* 2008;5:274-282.
50. Carmichael MG, Zacher LL. The demonstration of pulmonary neuroendocrine cell hyperplasia with tumorlets in a patient with chronic cough and a history of multiple medical problems. *Mil Med.* 2005;170:439-441.
51. Carvalho DR, Pinnola GC, Ferreira DRA, et al. Mandibular hypoplasia in fibrodysplasia ossificans progressiva causing obstructive sleep apnoea with pulmonary hypertension. *Clin Dysmorphol.* 2010;19:69-72.
52. Carvalho FR, Lentini-Oliveira DA, Carvalho GMM, Prado LBF, Prado GF, Carvalho LBC. Sleep-disordered breathing and orthodontic variables in children—Pilot study. *Int J Pediatr Otorhinolaryngol.* 2014;78:1965-1969. doi:http://dx.doi.org.login.ezproxy.library.ualberta.ca/10.1016/j.ijporl.2014.08.040.
53. Celenk M, Farrell M, Eren H, Kumar K, Singh G, Lozanoff S. Upper airway detection in cone beam images. *3rd International Conference on Bioinformatics and Biomedical Engineering, iCBBE 2009.* 2009 Accessed 25 April 2012.
54. Celenk M, Farrell ML, Eren H, Kumar K, Singh GD, Lozanoff S. Upper airway detection and visualization from cone beam image slices. *Journal of X-Ray Science and Technology.* 2010;18:121-135.
56. Cevidanes LHC, Heymann G, Cornelis MA, DeClerck HJ, Tulloch JFC. Superimposition of 3-dimensional cone-beam computed tomography models of growing patients. *American Journal of Orthodontics and Dentofacial Orthopedics.* 2009;136:94-99.
57. Cevidanes LHC, Motta A, Proffit WR, Ackerman JL, Styner M. Cranial base superimposition for 3-dimensional evaluation of soft-tissue changes. *American Journal of Orthodontics and Dentofacial Orthopedics.* 2010;137:S120-S129.

58. Cevidanes LHC, Oliveira AEF, Grauer D, Styner M, Proffit WR. Clinical application of 3D imaging for assessment of treatment outcomes. *Semin Orthod.* 2011;17:72-80.
59. Cevidanes LHS, Bailey LJ, Tucker Jr. GR, et al. Superimposition of 3D cone-beam CT models of orthognathic surgery patients. *Dentomaxillofacial Radiology.* 2005;34:369-375.
60. Cevidanes LHS, Styner MA, Proffit WR. Image analysis and superimposition of 3-dimensional cone-beam computed tomography models. *American Journal of Orthodontics and Dentofacial Orthopedics.* 2006;129:611-618.
61. Chan CS, Bye PTP, Woolcock AJ, Sullivan CE. Eucapnia and hypercapnia in patients with chronic airflow limitation. the role of the upper airway. *Am Rev Respir Dis.* 1990;141:861-865.
62. Chan CS, Grunstein RR, Bye PTP, Woolcock AJ, Sullivan CE. Obstructive sleep apnea with severe chronic airflow limitation. comparison of hypercapnic and eucapnic patients. *Am Rev Respir Dis.* 1989;140:1274-1278.
63. 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. *American Journal of Orthodontics and Dentofacial Orthopedics.* 2013;143:462-470.
66. Chen H, Lowe AA, Strauss AM, et al. Dental changes evaluated with a 3D computer-assisted model analysis after long-term tongue retaining device wear in OSA patients. *Sleep and Breathing.* 2008;12:169-178.
67. Chen N-, Li KK, Li S-, et al. Airway assessment by volumetric computed tomography in snorers and subjects with obstructive sleep apnea in a far-east asian population (chinese). *Laryngoscope.* 2002;112:721-726.
68. Chen Y-, Chen S-, Yao JC-, Chang H-. The effects of differences in landmark identification on the cephalometric measurements in traditional versus digitized cephalometry. *Angle Orthod.* 2004;74:155-161.
69. Cheng I, Nilufar S, Flores-Mir C, Basu A. Airway segmentation and measurement in CT images. *Conference proceedings : ...Annual International Conference of the IEEE Engineering in Medicine and Biology Society.IEEE Engineering in Medicine and Biology Society.Conference.* 2007;2007:795-799.
70. Chervin RD, Hedger K, Dillon JE, Pituch KJ. Pediatric sleep questionnaire (PSQ): Validity and reliability of scales for sleep-disordered breathing, snoring, sleepiness, and behavioral problems. *Sleep Med.* 2000;1:21-32.
71. Chirakalwasan N, Shim C, Appel D. Continuous positive airway pressure as a treatment modality for orthopnea in a patient with chronic obstructive pulmonary disease and extreme obesity undergoing left superficial femoral thrombectomy. *J Cardiothorac Vasc Anesth.* 2009;23:522-525.
72. Choi J-, Hur Y-, Lee J-, Clark GT. Effects of mandibular advancement on upper airway dimension and collapsibility in patients with obstructive sleep apnea using dynamic upper airway imaging during sleep. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontology.* 2010;109:712-719.

73. Choi J-, Kee W-, Lee J-, Ye M-. Variable site of oropharyngeal narrowing and regional variations of oropharyngeal collapsibility among snoring patients during wakefulness and sleep. *Cranio.* 2001;19:252-259.
74. Conley RS. Evidence for dental and dental specialty treatment of obstructive sleep apnoea. part 1: The adult OSA patient and part 2: The paediatric and adolescent patient. *J Oral Rehabil.* 2011;38:136-156.
75. Costa DJ, Mitchell R. Adenotonsillectomy for obstructive sleep apnea in obese children: A meta-analysis. *Otolaryngology - Head and Neck Surgery.* 2009;140:455-460.
76. Cozza P, Ballanti F, Castellano M, Fanucci E. Role of computed tomography in the evaluation of orthodontic treatment in adult patients with obstructive sleep apnea syndrome (OSA). *Progress in orthodontics.* 2008;9:6-16.
77. Crumley RL, Stein M, Gamsu G. Determination of obstructive site in obstructive sleep apnea. *Laryngoscope.* 1987;97:301-308.
78. da Motta ATS, Carvalho FAR, Oliveira AEF, Cevidanes LHS, Almeida MAO. Superimposition of 3D cone-beam CT models in orthognathic surgery. *Dental Press Journal of Orthodontics.* 2010;15:39-41.
79. Davis KA, Cantor C, Maus D, Herman ST. A neurological cause of recurrent choking during sleep. *Journal of Clinical Sleep Medicine.* 2008;4:586-587.
80. De Backer JW, Vos WG, Verhulst SL, De Backer W. Novel imaging techniques using computer methods for the evaluation of the upper airway in patients with sleep-disordered breathing: A comprehensive review. *Sleep Medicine Reviews.* 2008;12:437-447.
81. de Water VR, Saridin JK, Bouw F, Murawska MM, Koudstaal MJ. 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.
82. DeCesare A, Secanell M, Lagravère MO, Carey J. Multiobjective optimization framework for landmark measurement error correction in three-dimensional cephalometric tomography. *Dentomaxillofacial Radiology.* 2013;42.
83. Decker MJ, Haaga J, Arnold JL, Atzberger D, Strohl KP. Functional electrical stimulation and respiration during sleep. *J Appl Physiol.* 1993;75:1053-1061.
84. Deeb W, Hansen L, Hotan T, Hietschold V, Harzer W, Tausche E. Changes in nasal volume after surgically assisted bone-borne rapid maxillary expansion. *American Journal of Orthodontics and Dentofacial Orthopedics.* 2010;137:782-789.
85. Dempsey JA, Veasey SC, Morgan BJ, O'Donnell CP. Pathophysiology of sleep apnea. *Physiol Rev.* 2010;90:47-112.
86. DePonte F, Sassano P, Gennaro P, Pascali M, Marchetti E. Obstructive sleep apnea in a growing patient. *J Craniofac Surg.* 1999;10:430-434.
87. Desseilles M, Dang-Vu T, Schabus M, Sterpenich V, Maquet P, Schwartz S. Neuroimaging insights into the pathophysiology of sleep disorders. *Sleep.* 2008;31:777-794.

89. Di Carlo G, Polimeni A, Melsen B, Cattaneo PM. The relationship between upper airways and craniofacial morphology studied in 3D. A CBCT study. *Orthodontics and Craniofacial Research.* 2015;18:1-11.
90. DiMario Jr. FJ. Brainstem tubers presenting as disordered breathing in tuberous sclerosis complex. *J Child Neurol.* 1995;10:407-409.
91. Ding Q, Xing N, Wang J-. Multi-slice spiral CT and airway reconstruction in 33 patients with obstructive sleep apnea syndrome. *Journal of Clinical Rehabilitative Tissue Engineering Research.* 2007;11:4420-4421.
92. Djupesland G, Schrader H, Lyberg T, Refsum H, Lilleas F, Godtlibsen OB. Palatopharyngoglossoplasty in the treatment of patients with obstructive sleep apnea syndrome. *Acta Oto-Laryngologica, Supplement.* 1992:50-54.
93. Dos Santos VM, De Paula FH, Filho JAS. Respiratory changes in prader-willi syndrome. *Singapore Med J.* 2009;50:107.
94. Edmonds LC, Daniels BK, Stanson AW, Sheedy II PF, Shepard Jr. JW. The effects of transcutaneous electrical stimulation during wakefulness and sleep in patients with obstructive sleep apnea. *Am Rev Respir Dis.* 1992;146:1030-1036.
95. Efendiyeva R, Aydemir H, Karasu H, Toygar-Memikoɨlu U. Pharyngeal airway space, hyoid bone position, and head posture after bimaxillary orthognathic surgery in class III patients long-term evaluation. *Angle Orthod.* 2014;84:773-781.
96. El Amm CA, Denny A. Hyoid bone abnormalities in pierre robin patients. *J Craniofac Surg.* 2008;19:259-263.
97. El Fortia M, El Fagieh M, Khalil M, Elhamroush H, Eldergash O, El Gatit A. A massive retropharyngeal lipoma. *European Journal of Radiology Extra.* 2006;57:9-12.
99. El AS, El H, Palomo JM, Baur DA. A 3-dimensional airway analysis of an obstructive sleep apnea surgical correction with cone beam computed tomography. *Journal of Oral and Maxillofacial Surgery.*;In Press, Corrected Proof doi:DOI: 10.1016/j.joms.2010.11.046.
100. El H, Palomo JM. Measuring the airway in 3 dimensions: A reliability and accuracy study. *American Journal of Orthodontics and Dentofacial Orthopedics.* 2010;137:S50.e1-S50.e9.
101. El H, Palomo JM. Editor's comment and Q&A: Measuring the airway in 3 dimensions: A reliability and accuracy study. *American Journal of Orthodontics and Dentofacial Orthopedics.* 2010;137:S50-S52. doi:http://dx.doi.org/10.1016/j.ajodo.2010.01.014.
102. Eloy JA, Carneiro E, Vibhute P, Genden EM, Bederson JB, Som PM. A rare prevertebral ordinary lipoma presenting as obstructive sleep apnea: Computed tomographic and magnetic resonance imaging findings. *Archives of Otolaryngology - Head and Neck Surgery.* 2008;134:1001-1003.
103. Eloy JA, Omerhodzic S, Som PM, Genden EM. Goitrous hashimoto's thyroiditis presenting as obstructive sleep apnea. *Thyroid.* 2007;17:691-692.
104. Enciso R, Memon A, Mah J. Three-dimensional visualization of the craniofacial patient: Volume segmentation, data integration and animation. *Orthodontics & craniofacial research.* 2003;6 Suppl 1:66-71; discussion 179.

105. Enciso R, Nguyen M, Shigeta Y, Ogawa T, Clark GT. Comparison of cone-beam CT parameters and sleep questionnaires in sleep apnea patients and control subjects. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontology.* 2010;109:285-293.
106. Enoz M. Computed tomography scan of the upper airway is not practical and cost-effective for using every patient with obstructive sleep apnea [1]. *Otolaryngology - Head and Neck Surgery.* 2006;134:537.
107. Epstein MD, Segal LN, Ibrahim SM, Friedman N, Bustami R. Snoring and the risk of obstructive sleep apnea in patients with pulmonary embolism. *Sleep.* 2010;33:1069-1074.
108. Eskandar EN, Loeffler JS, O'Neill AM, Hunter GJ, Louis DN. Case 33-2004: A 34-year-old man with a seizure and a frontal-lobe brain lesion. *N Engl J Med.* 2004;351:1875-1882.
109. Espinosa G, Alarcón A, Morelló A, Vilaseca I, Ayuso JR, Montserrat JM. Obstructive sleep apnea syndromes (OSAS) secondary to pharyngeal lymphoma. *Arch Bronconeumol.* 1996;32:547-549.
110. Eun YJ, Woo ST, Sun JH, Cho J-, Seung BH. Reduced cerebral blood flow during wakefulness in obstructive sleep apnea-hypopnea syndrome. *Sleep.* 2007;30:1515-1520.
111. Ezcurra Hernández P, Albertí I Casas A, Figuerola Massana E, et al. Laryngeal sarcoidosis: A case report. *Acta Otorrinolaringol Esp.* 2003;54:117-120.
112. Faber CE, Grymer L. Available techniques for objective assessment of upper airway narrowing in snoring and sleep apnea. *Sleep and Breathing.* 2003;7:77-86.
113. Fairburn SC, Waite PD, Vilos G, et al. Three-dimensional changes in upper airways of patients with obstructive sleep apnea following maxillomandibular advancement. *Journal of Oral and Maxillofacial Surgery.* 2007;65:6-12.
114. Fajdiga I. Snoring imaging could bernoulli explain it all? *Chest.* 2005;128:896-901.
115. Farnaz S, Gothi D, Joshi JM. Acromesomelic dysplasia with bronchiectasis. *Indian J Chest Dis Allied Sci.* 2005;47:131-134.
116. Feiyun P, Wei L, Jun C, Xin X, Zhuojin S, Fengguo Y. Simultaneous correction of bilateral temporomandibular joint ankylosis with mandibular micrognathia using internal distraction osteogenesis and 3-dimensional craniomaxillofacial models. *Journal of Oral and Maxillofacial Surgery.* 2010;68:571-577.
117. Ferretti G, Pépin JL, Lévy P. Imaging in obstructive sleep apnea syndrome. *Rev Neurol.* 2001;157:S78-81.
118. Ficker JH, Feistel H, Möller C, et al. Changes in regional cerebral perfusion in patients with obstructive sleep apnoea syndrome - first studies with nocturnal 99mTc-HMPAO SPECT. *Pneumologie.* 1997;51:926-930.
119. Fiorillo JA. Merkel cell carcinoma metastatic to the heart. *Journal of Clinical Oncology.* 2008;26:3643-3644.
120. Fishman AP, Palevsky HI. Pulmonary hypertension and chronic cor pulmonale. *Heart Disease and Stroke.* 1993;2:335-341.
121. Fleetham JA. Upper airway imaging in relation to obstructive sleep apnea. *Clin Chest Med.* 1992;13:399-416.

122. Flemons W, Littner M, Rowley J, et al. Home diagnosis of sleep apnea: A systematic review of the literature. an evidence review cosponsored by the american academy of sleep medicine, the american college of chest physicians, and the american thoracic society. *Chest.* 2003;124:1543-79.
123. Flores RL, Shetye PR, Zeitler D, et al. Airway changes following le fort III distraction osteogenesis for syndromic craniosynostosis: A clinical and cephalometric study. *Plast Reconstr Surg.* 2009;124:590-601.
124. Franco Jr. RA, Rosenfeld RM, Rao M. Quality of life for children with obstructive sleep apnea. *Otolaryngology - Head and Neck Surgery.* 2000;123:9-16.
125. Fricke BL, Donnelly LF, Shott SR, et al. Comparison of lingual tonsil size as depicted on MR imaging between children with obstructive sleep apnea despite previous tonsillectomy and adenoidectomy and normal controls. *Pediatr Radiol.* 2006;36:518-523.
126. Friedman M, Lin H-, Gurpinar B, Joseph NJ. Minimally invasive single-stage multilevel treatment for obstructive sleep apnea/hypopnea syndrome. *Laryngoscope.* 2007;117:1859-1863.
127. Friedman M, Wilson M, Lin H-, Chang H-. Updated systematic review of tonsillectomy and adenoidectomy for treatment of pediatric obstructive sleep apnea/hypopnea syndrome. *Otolaryngology - Head and Neck Surgery.* 2009;140:800-808.
128. Friedman M, Wilson MN, Pulver TM, et al. Measurements of adult lingual tonsil tissue in health and disease. *Otolaryngology - Head and Neck Surgery.* 2010;142:520-525.
129. Fung E, Cave D, Witmans M, Gan K, El-Hakim H. Postoperative respiratory complications and recovery in obese children following adenotonsillectomy for sleep-disordered breathing: A case-control study. *Otolaryngology - Head and Neck Surgery.* 2010;142:898-905.
130. Gale DJ, Sawyer RH, Woodcock A, Stone P, Thompson R, O'Brien K. Do oral appliances enlarge the airway in patients with obstructive sleep apnoea? A prospective computerized tomographic study. *Eur J Orthod.* 2000;22:159-168.
131. Galvin JR, Rooholamini SA, Stanford W. Obstructive sleep apnea: Diagnosis with ultrafast CT. *Radiology.* 1989;171:775-778.
132. Gao P, Li W-, Shen P, et al. Comparative study of determining the site of airway obstruction in obstructive sleep apnea-hypopnea between MSCT and airway press measurements. *Chinese Journal of Medical Imaging Technology.* 2007;23:1784-1788.
133. Gebeile-Chauty S, Pelosse JJ, Diemunsch C. [Specific aspects of diagnosis. importance of the clinical examination and supplementary examinations]. *L' Orthodontie française.* 2011;82:27-38.
134. Georgalas C, Garas G, Hadjihannas E, Oostra A. Assessment of obstruction level and selection of patients for obstructive sleep apnoea surgery: An evidence-based approach. *J Laryngol Otol.* 2010;124:1-9.
136. George LT, Barber HD, Smith BM. Maxillomandibular advancement surgery: An alternative treatment option for obstructive sleep apnea. *Atlas Oral Maxillofac Surg Clin North Am.* 2007;15:163-177.

137. Ghoneima A, Kula K. Accuracy and reliability of cone-beam computed tomography for airway volume analysis. *Eur J Orthod.* 2013;35:256-261.
138. Giannoni C, Sulek M, Friedman EM, Duncan III NO. Acquired nasopharyngeal stenosis: A warning and review. *Archives of Otolaryngology - Head and Neck Surgery.* 1998;124:163-167.
139. Giddings CEB, Bray D, Rimmer J, Williamson P. Pleomorphic adenoma and severe obstructive sleep apnoea. *J Laryngol Otol.* 2005;119:226-229.
140. Gilman S, Chervin RD, Koeppe RA, et al. Obstructive sleep apnea is related to a thalamic cholinergic deficit in MSA. *Neurology.* 2003;61:35-39.
141. Gionhaku N, Lowe AA. Relationship between jaw muscle volume and craniofacial form. *J Dent Res.* 1989;68:805-809.
142. Gold DR, Annino Jr. DJ. HIV-associated cervicodorsal lipodystrophy: Etiology and management. *Laryngoscope.* 2005;115:791-795.
143. Gong W, Wang E, Zhang B, Da J. A retropharyngeal lipoma causing obstructive sleep apnea in a child. *Journal of Clinical Sleep Medicine.* 2006;2:328-329.
144. Gonzalez R, Woods R. *Digital Image Processing*
. 3rd ed. Prentice Hall; 2007.
145. Grauer D, Cevidanes LSH, Styner MA, Ackerman JL, Proffit WR. Pharyngeal airway volume and shape from cone-beam computed tomography: Relationship to facial morphology. *American Journal of Orthodontics and Dentofacial Orthopedics.* 2009;136:805-814.
146. Gugger M, Vock P. Effect of reduced expiratory pressure on pharyngeal size during nasal positive airway pressure in patients with sleep apnoea: Evaluation by continuous computed tomography. *Thorax.* 1992;47:809-813.
147. 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;42:1140-1149.
148. Guilleminault C. Obstructive sleep apnea. the clinical syndrome and historical perspective. *Med Clin North Am.* 1985;69:1187-1203.
149. Guilleminault C, Ji HL, Chan A. Pediatric obstructive sleep apnea syndrome. *Archives of Pediatrics and Adolescent Medicine.* 2005;159:775-785.
150. Guilleminault C, Li K, Quo S, Inouye RN. A prospective study on the surgical outcomes of children with sleep-disordered breathing. *Sleep.* 2004;27:95-100.
151. Guilleminault C, Li KK, Khramtsov A, Pelayo R, Martinez S. Sleep disordered breathing: Surgical outcomes in prepubertal children. *Laryngoscope.* 2004;114:132-137.
152. Guilleminault C, Powel N, Heldt G, Riley R. Small upper airway in near-miss sudden infant death syndrome infants and their families. *Lancet.* 1986;1:402-407.
153. Gupta V, Singh H, Gupta M, Singh S. Dislocation of the inferior turbinates: A rare complication of nasal surgery, presenting as obstructive sleep apnoea. *J Laryngol Otol.* 2011;125:859-860.
154. Gutierrez T, Leong AC, Pang L, Chevretton E, Jeannon J-, Simo R. Multinodular thyroid goitre causing obstructive sleep apnoea syndrome. *J Laryngol Otol.* 2012;126:190-195.

155. Hanigan WC, Zallek SN, Pickard JD, Milhorat TH, Bergsneider M, Kelly DF. Headaches, shunts, and obstructive sleep apnea: Report of two cases. *Neurosurgery.* 2004;54:764-769.
156. Hannon TS, Lee S, Chakravorty S, Lin Y, Arslanian SA. Sleep-disordered breathing in obese adolescents is associated with visceral adiposity and markers of insulin resistance. *International Journal of Pediatric Obesity.* 2011;6:157-160.
157. Haponik EF, Smith PL, Bohlman ME. Computerized tomography in obstructive sleep apnea. correlation of airway size with physiology during sleep and wakefulness. *Am Rev Respir Dis.* 1983;127:221-226.
158. Harbison J, Gibson GJ, Birchall D, Zammit-Maempel I, Ford GA. White matter disease and sleep-disordered breathing after acute stroke. *Neurology.* 2003;61:959-963.
159. Hardin RE, Brevetti GR, Sanusi M, et al. Treatment of symptomatic vascular rings in the elderly. *Texas Heart Institute Journal.* 2005;32:411-415.
160. Harper D, Bloom DA, Rowley JA, Soubani A, Smith WL. The high-resolution chest CT findings in an adult with melnick-needles syndrome. *Clin Imaging.* 2006;30:350-353.
161. Harsch IA, Schahin SP, Fuchs FS, et al. Insulin resistance, hyperleptinemia, and obstructive sleep apnea in launois-bensaude syndrome. *Obes Res.* 2002;10:625-632.
163. Haskell JA, McCrillis J, Haskell BS, Scheetz JP, Scarfe WC, Farman AG. Effects of mandibular advancement device (MAD) on airway dimensions assessed with cone-beam computed tomography. *Semin Orthod.* 2009;15:132-158. doi:DOI: 10.1053/j.sodo.2009.02.001.
164. Hatcher DC. Cone beam computed tomography: Craniofacial and airway analysis. *Dent Clin North Am.* 2012;56:343-357.
165. Hatcher DC. Cone beam computed tomography: Craniofacial and airway analysis. *Sleep Medicine Clinics.* 2010;5:59-70.
167. Helfaer MA, Wilson MD. Obstructive sleep apnea, control of ventilation, and anesthesia in children. *Pediatr Clin North Am.* 1994;41:131-151.
168. Heo J-, Kim J-. Correlation between severity of sleep apnea and upper airway morphology: Cephalometry and MD-CT study during awake and sleep states. *Acta Otolaryngol.* 2010;131:84-90.
169. Herer B, Royand F, Kieffer E, Vincent JP. A case report of an obesity hypoventilation syndrome associated with obstructive sleep apnea due to a carotid body paraganglioma. *Sleep Med.* 2003;4:459-463.
170. Herzog M, Schmidt A, Metz T, et al. Pseudoaneurysm of the lingual artery after temperature-controlled radiofrequency tongue base reduction: A severe complication. *Laryngoscope.* 2006;116:665-667.
171. Hoch S, Mayer C, Teymoortash A, Werner JA. Snoring in oropharyngeal and nasopharyngeal pulsations. *Laryngorhinootologie.* 2010;89:752-753.
172. Hochman MS, Chediak AD, Ziffer JA. Hyperekplexia: Report of a nonfamilial adult onset case associated with obstructive sleep apnea and abnormal brain nuclear tomography. *Sleep.* 1994;17:280-283.

173. Hockstein NG, Anderson TA, Moonis G, Gustafson KS, Mirza N. Retropharyngeal lipoma causing obstructive sleep apnea: Case report including five-year follow-up. *Laryngoscope.* 2002;112:1603-1605.
174. Hoffstein V. Review of oral appliances for treatment of sleep-disordered breathing. *Sleep and Breathing.* 2007;11:1-22.
175. Höl M, Bauknecht HC, Fietze I, Seidner W, Reinhardt A, Scheret H. Problems of hyomandibulopexia in patients with OSAS. *Laryngorhinootologie.* 2006;85:715-719.
176. Hooper RG, Kemp SF, DeShazo R, Rappai M, Collop N. Nasal airflow in sleep-disordered breathing [6] (multiple letters). *Chest.* 2004;126:316-317.
177. Horner RL, Shea SA, McIvor J, Guz A. Pharyngeal size and shape during wakefulness and sleep in patients with obstructive sleep apnoea. *Q J Med.* 1989;72:719-735.
178. Hou T, Shao J, Fang S. The definition of the v zone for the safety space of functional surgery of the tongue. *Laryngoscope.* 2012;122:66-70.
179. Hou T-, Zhou L-, Hu H-. Computed tomographic angiography study of the relationship between the lingual artery and lingual markers in patients with obstructive sleep apnoea. *Clin Radiol.* 2011;66:526-529.
180. Hsu P, Han H, Chan Y, et al. Quantitative computer-assisted digital-imaging upper airway analysis for obstructive sleep apnoea. *Clin Otolaryngol Allied Sci.* 2004;29:522-529.
181. Hu JB, Hu HJ, Hou TN, Gao HX, He J. [Localization of upper airway stricture by CT scan in patients with obstructive sleep apnea syndrome during drug-induced sleeping]. *Zhejiang da xue xue bao.Yi xue ban = Journal of Zhejiang University.Medical sciences.* 2010;39:168-173.
182. Huang Y-, Guilleminault C, Lee LA, Lin C-, Hwang F-. Treatment outcomes of adenotonsillectomy for children with obstructive sleep apnea: A prospective longitudinal study. *Sleep.* 2014;37:71-76.
183. Hultcrantz E, Löfstrand Tideström B. The development of sleep disordered breathing from 4 to 12 years and dental arch morphology. *Int J Pediatr Otorhinolaryngol.* 2009;73:1234-1241.
184. Huynh J, Kim D, McQuilling M. Pharyngeal airflow analysis in obstructive sleep apnea patients pre- and post-maxillomandibular advancement surgery. *J of fluids Eng.* 2009;131:091101-091111.
185. Huynh NT, Morton PD, Rompré PH, Papadakis A, Remise C. Associations between sleep-disordered breathing symptoms and facial and dental morphometry, assessed with screening examinations. *American Journal of Orthodontics and Dentofacial Orthopedics.* 2011;140:762-770.
186. Hwang D-, Kim Y-, Park S-, Lee J-. Midfacial soft tissue changes after leveling le fort I osteotomy with differential reduction: Cone-beam computed tomography volume superimposition. *Angle Orthod.* 2012;82:424-431.
187. Iannetti G, Polimeni A, Pagnoni M, et al. Upper airway volume after le fort III advancement in subjects with craniofacial malformation.. *J Craniofac Surg.* 2011;22:351-5.
189. Ioachimescu OC, Collop NA. Sleep-disordered breathing. *Neurol Clin.* 2012;30:1095-1136.

190. Ip MSM, Tan KCB, Peh WCG, Lam KSL. Effect of sandostatin® LAR® on sleep apnoea in acromegaly: Correlation with computerized tomographic cephalometry and hormonal activity. *Clin Endocrinol (Oxf).* 2001;55:477-483.
191. Ireland PJ, Johnson S, Donaghey S, et al. Medical management of children with achondroplasia: Evaluation of an australasian cohort aged 0-5years. *J Paediatr Child Health.* 2011.
192. Ito Y, Cheng GC, Shih AM, et al. Patient-specific geometry modeling and mesh generation for simulating obstructive sleep apnea syndrome cases by maxillomandibular advancement. *Math Comput Simul.* 2011;81:1876-1891.
193. Iwasaki T, Hayasaki H, Takemoto Y, Kanomi R, Yamasaki Y. Oropharyngeal airway in children with class III malocclusion evaluated by cone-beam computed tomography. *American Journal of Orthodontics and Dentofacial Orthopedics.* 2009;136:318.e1-318.e9.
194. Iwasaki T, Saitoh I, Takemoto Y, et al. Evaluation of upper airway obstruction in class II children with fluid-mechanical simulation. *American Journal of Orthodontics and Dentofacial Orthopedics.* 2011;139:e135-e145.
195. Jackman AR, Biggs SN, Walter LM, et al. Sleep-disordered breathing in preschool children is associated with behavioral, but not cognitive, impairments. *Sleep Med.* 2012.
196. Jacob SS, Jacob JJ, Paul TV. Foreign body aspiration in a boy with prader-willi syndrome. *Singapore Med J.* 2008;49:e12-e14.
197. Janson C, Gislason T, Bengtsson H, et al. Long-term follow-up of patients with obstructive sleep apnea treated with uvulopalatopharyngoplasty. *Archives of Otolaryngology - Head and Neck Surgery.* 1997;123:257-262.
198. Jeong S-, Kim W-, Sung S-. Numerical investigation on the flow characteristics and aerodynamic force of the upper airway of patient with obstructive sleep apnea using computational fluid dynamics. *Medical Engineering and Physics.* 2007;29:637-651.
199. Jia P, Fu M, Zeng X. Changes of upper airway morphology induced by mandibular advancement in patients with obstructive sleep apnea syndrome. *Beijing da xue xue bao.Yi xue ban = Journal of Peking University.Health sciences.* 2003;35:663-667.
200. Jiang M, Zhou M, Huang W, et al. [The study of resilience of oral pharyngeal wall in patients with obstructive sleep apnea hypopnea syndrome applied with multiple detector-row spiral CT]. *Lin chuang er bi yan hou tou jing wai ke za zhi = Journal of clinical otorhinolaryngology, head, and neck surgery.* 2007;21:97-99.
201. Kairaitis K, Howitt L, Wheatley JR, Amis TC. Mass loading of the upper airway extraluminal tissue space in rabbits: Effects on tissue pressure and pharyngeal airway lumen geometry. *J Appl Physiol.* 2009;106:887-892.
202. Kaiser P. Obstructive sleep apnea in poorly controlled asthmatic children: Effect of adenotonsillectomy. *Pediatr Pulmonol.* 2012;47:311.
203. Kalra A, Abouzgheib W, Gajera M, Palaniswamy C, Puri N, Dellinger RP. Excessive dynamic airway collapse for the internist: New nomenclature or different entity? *Postgrad Med J.* 2011;87:482-486.

204. Kamata S, Kamiyama M, Sawai T, et al. Assessment of obstructive apnea by using polysomnography and surgical treatment in patients with beckwith-wiedemann syndrome. *J Pediatr Surg.* 2005;40:E17-E19.
205. Kapelushnik J, Shalev H, Schulman H, Moser A, Tamary H. Upper airway obstruction-related sleep apnea in a child with thalassemia intermedia. *Journal of Pediatric Hematology/Oncology.* 2001;23:525-526.
206. Karimi M, Koranyi J, Franco C, et al. Increased neck soft tissue mass and worsening of obstructive sleep apnea after growth hormone treatment in men with abdominal obesity. *Journal of Clinical Sleep Medicine.* 2010;6:256-263.
207. Katz ES, D'Ambrosio CM. Pathophysiology of pediatric obstructive sleep apnea. *Proceedings of the American Thoracic Society.* 2008;5:253-262.
208. Kelly DH, Krishnamoorthy KS, Shannon DC. Astrocytoma in an infant with prolonged apnea. *Pediatrics.* 1980;66:429-431.
209. Khan NU, Babb JD, Kaul S, Williams JM, Miller MJ. A novel complication of bariatric surgery. *The American heart hospital journal.* 2009;7:69-71.
210. Kim EJ, Choi JH, Kim KW, et al. The impacts of open-mouth breathing on upper airway space in obstructive sleep apnea: 3-D MDCT analysis. *European Archives of Oto-Rhino-Laryngology.* 2011;268:533-539.
211. Kim N, Joon BS, Song K-, Eun JC, Kang S-. Semi-automatic measurement of the airway dimension by computed tomography using the full-with-half-maximum method: A study of the measurement accuracy according to the orientation of an artificial airway. *Korean Journal of Radiology.* 2008;9:236-242.
212. Kim SH, Cho G-, Baik I, et al. Association of coronary artery calcification with obstructive sleep apnea and obesity in middle-aged men. *Nutrition, Metabolism and Cardiovascular Diseases.* 2010;20:575-582.
213. Kim TS, Caruso JM, Christensen H, Torabinejad M. A comparison of cone-beam computed tomography and direct measurement in the examination of the mandibular canal and adjacent structures. *J Endod.* 2010;36:1191-1194.
214. Kim YI, Kim JR, Park SB. Three-dimensional analysis of midfacial soft tissue changes according to maxillary superior movement after horizontal osteotomy of the maxilla. *J Craniofac Surg.* 2010;21:1587-1590.
215. Kim Y-, Park S-, Son W-, Hwang D-. Midfacial soft-tissue changes after advancement of maxilla with le fort I osteotomy and mandibular setback surgery: Comparison of conventional and high le fort I osteotomies by superimposition of cone-beam computed tomography volumes. *Journal of Oral and Maxillofacial Surgery.* 2011;69:e225-e233.
216. Kim Y-, Hong J-, Hwang Y-, Park Y-. Three-dimensional analysis of pharyngeal airway in preadolescent children with different anteroposterior skeletal patterns. *American Journal of Orthodontics and Dentofacial Orthopedics.* 2010;137:306.e1-306.e11.

217. Kitcher ED, Searyoh K, Abaidoo B. Quality of life outcomes of adenotonsillectomy for obstructive sleep disorders: Our experience in a tertiary care centre in ghana. *West Afr J Med.* 2013;32:139-144.
218. Knutson KL, Zhao X, Mattingly M, Galli G, Cizza G. Predictors of sleep-disordered breathing in obese adults who are chronic short sleepers. *Sleep Med.* 2012;13:484-489. doi:10.1016/j.sleep.2011.11.009.
219. Kobayashi R, Miyazaki S, Karaki M, et al. Evaluation of adenotonsillectomy and tonsillectomy for pediatric obstructive sleep apnea by rhinomanometry and the OSA-18 questionnaire. *Acta Otolaryngol.* 2014;134:818-823.
220. Kobayashi R, Miyazaki S, Karaki M, et al. Evaluation of adenotonsillectomy and tonsillectomy for pediatric obstructive sleep apnea by rhinomanometry and the OSA-18 questionnaire. *Acta Otolaryngol.* 2014;134:818-823.
221. Koch GG. Intraclass correlation coefficient In: *Encyclopedia of Statistical Sciences* 4th ed. New York: Samuel Kotz and Norman L. Johnson. John Wiley & Sons.:213-217.
222. Koopman Jr. CF, Moran Jr. WB. Surgical management of obstructive sleep apnea. *Otolaryngol Clin North Am.* 1990;23:787-808.
223. Koren A, Grošelj LD, Fajdiga I. CT comparison of primary snoring and obstructive sleep apnea syndrome: Role of pharyngeal narrowing ratio and soft palate-tongue contact in awake patient. *European Archives of Oto-Rhino-Laryngology.* 2009;266:727-734.
224. Kourelis K, Gouma P, Naxakis S, Kalogeropoulou C, Goumas P. Oculoauriculovertebral complex with an atypical cause of obstructive sleep apnea. *Int J Pediatr Otorhinolaryngol.* 2009;73:481-485.
225. Kuna ST, Bedi DG, Ryckman C. Effect of nasal airway positive pressure on upper airway size and configuration. *Am Rev Respir Dis.* 1988;138:969-975.
226. Kurashima K, Takayanagi N, Sato N, et al. High resolution CT and bronchial reversibility test for diagnosing COPD. *Respirology.* 2005;10:316-322.
227. Kurihara M, Kumagai K, Goto K, Imai M, Yagishita S. Severe type hunter's syndrome. polysomnographic and neuropathological study. *Neuropediatrics.* 1992;23:248-256.
228. Kuzniar TJ, Gruber B, Mutlu GM. Cerebrospinal fluid leak and meningitis associated with nasal continuous positive air-way pressure therapy. *Chest.* 2005;128:1882-1884.
229. Kyung SH, Park Y-, Pae E-. Obstructive sleep apnea patients with the oral appliance experience pharyngeal size and shape changes in three dimensions. *Angle Orthod.* 2005;75:15-22.
230. Łabuz-Roszak B, Tazbirek M, Pierzchała K, Pierzchała W. Frequency of sleep apnea syndrome in patients with acute stroke. *Polski Merkuriusz Lekarski.* 2004;16:536-538.
231. Lagravère MO, Gordon JM, Guedes IH, et al. Reliability of traditional cephalometric landmarks as seen in three-dimensional analysis in maxillary expansion treatments. *Angle Orthod.* 2009;79:1047-1056.

232. Lagravère MO, Hansen L, Harzer W, Major PW. Plane orientation for standardization in 3-dimensional cephalometric analysis with computerized tomography imaging. *American Journal of Orthodontics and Dentofacial Orthopedics.* 2006;129:601-604.
233. Lagravère MO, Low C, Flores-Mir C, et al. Intraexaminer and interexaminer reliabilities of landmark identification on digitized lateral cephalograms and formatted 3-dimensional cone-beam computerized tomography images. *American Journal of Orthodontics and Dentofacial Orthopedics.* 2010;137:598-604.
234. Lagravère MO, Major PW, Carey J. Sensitivity analysis for plane orientation in three-dimensional cephalometric analysis based on superimposition of serial cone beam computed tomography images. *Dentomaxillofacial Radiology.* 2010;39:400-408.
235. Lagravere M, Major P, Flores-Mir C. Long-term skeletal changes with rapid maxillary expansion: A systematic review. *Angle Orthod.* 2005;75:833-9.
236. Lagravre MO, Gordon JM, Flores-Mir C, Carey J, Heo G, Major PW. Cranial base foramen location accuracy and reliability in cone-beam computerized tomography. *American Journal of Orthodontics and Dentofacial Orthopedics.* 2011;139:e203-e210.
237. Lagravre MO, Secanell M, Major PW, Carey JP. Optimization analysis for plane orientation in 3-dimensional cephalometric analysis of serial cone-beam computerized tomography images. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontology.* 2011;111:771-777.
238. Lakadamyali H, Ergun T, Lakadamyali H, Avci S. A giant retropharyngeal lipoma showing no change in clinical presentation and size within a two-year follow-up: A case report. *Kulak burun boğaz ihtisas dergisi : KBB = Journal of ear, nose, and throat.* 2008;18:374-376.
239. Lam B, Ooi CGC, Peh WCG, et al. Computed tomographic evaluation of the role of craniofacial and upper airway morphology in obstructive sleep apnea in chinese. *Respir Med.* 2004;98:301-307.
240. Lan Z, Itoi A, Takashima M, Oda M, Tomoda K. Difference of pharyngeal morphology and mechanical property between OSAHS patients and normal subjects. *Auris Nasus Larynx.* 2006;33:433-439.
241. Larsson S-, Gislason T, Lindholm CE. Computed tomography of the oropharynx in obstructive sleep apnea. *Acta Radiol.* 1988;29:401-405.
242. Lee C-, Kang K-, Weng W-, Lee P-, Hsu W-. Quality of life after adenotonsillectomy in children with obstructive sleep apnea: Short-term and long-term results. *Int J Pediatr Otorhinolaryngol.* 2015;79:210-215.
243. Lee C-, Kang K-, Weng W-, Lee P-, Hsu W-. Quality of life after adenotonsillectomy for children with sleep-disordered breathing: A linear mixed model analysis. *Int J Pediatr Otorhinolaryngol.* 2014;78:1374-1380.
244. Lee D-. Measurements of adult lingual tonsil tissue in health and disease. *Otolaryngology - Head and Neck Surgery.* 2010;143:172-173.

245. Lee SH, Kim EJ, Choi JH, et al. Upper airway changes in severe obstructive sleep apnea: Upper airway length and volumetric analyses using 3D MDCT. *Acta Otolaryngol.* 2011;131:527-532.
246. Lenza MG, de O. Lenza MM, Dalstra M, Melsen B, Cattaneo PM. An analysis of different approaches to the assessment of upper airway morphology: A CBCT study. *Orthodontics and Craniofacial Research.* 2010;13:96-105.
247. Leslie WD, Wali S, Kryger M, Netzer NC, Strohl KP. Blood flow of the middle cerebral artery with sleep-disordered breathing: Correlation with obstructive hypopneas [5] (multiple letters). *Stroke.* 1999;30:188-190.
248. Levendowski DJ, Morgan T, Montague J, Melzer V, Berka C, Westbrook PR. Prevalence of probable obstructive sleep apnea risk and severity in a population of dental patients. *Sleep and Breathing.* 2008;12:303-309.
249. Li B, Zhao L, Wang H, Xiu Q, Shenn J, Zhang H. [The effect of CPAP on the structure and function of upper airway of mini pig with OSAS]. *Sheng Wu Yi Xue Gong Cheng Xue Za Zhi.* 2007;24:631-635.
250. Li H-, Chen N-, Wang C-, Shu Y-, Wang P-. Use of 3-dimensional computed tomography scan to evaluate upper airway patency for patients undergoing sleep-disordered breathing surgery. *Otolaryngology - Head and Neck Surgery.* 2003;129:336-342.
251. Li H-, Li KK, Chen N-, Wang C-, Liao Y-, Wang P-. Three-dimensional computed tomography and polysomnography findings after extended uvulopalatal flap surgery for obstructive sleep apnea. *American Journal of Otolaryngology - Head and Neck Medicine and Surgery.* 2005;26:7-11.
252. Li H-, Wang P-, Hsu C-, Chen N-, Lee L-, Fang T-. Same-stage palatopharyngeal and hypopharyngeal surgery for severe obstructive sleep apnea. *Acta Otolaryngol.* 2004;124:820-826.
253. Li S, Dong X, Shi H, et al. Localization of upper airway stricture in patients with obstructive sleep apnea syndrome by CT scan. *Chung Hua Erh Pi Yen Hou Ko Tsa Chih.* 2002;37:133-136.
254. Li S, Gao L, Zou M, et al. [The effects of pressure level in veil on upper airway in patients with obstructive sleep apnea hypopnea syndrome]. *Lin chuang er bi yan hou tou jing wai ke za zhi = Journal of clinical otorhinolaryngology, head, and neck surgery.* 2008;22:673-677.
255. Li S, Qu S, Dong X, et al. The upper airway CT scan in patients with obstructive sleep apnea syndrome. *Lin Chuang Er Bi Yan Hou Ke Za Zhi.* 2002;16:280-282.
256. Li S, Shi H, Dong X, Qu S, Dong W, Wang G. Quantitative evaluation of the upper airway by CT scan with the muller maneuver. *Lin chuang er bi yan hou ke za zhi = Journal of clinical otorhinolaryngology.* 2005;19:104-107.
257. Li S, Shi H, Qü S, Hua Z, Dong X, Dong W. The lingual region upper airway CT scan of obstructive sleep apnea patients. *Zhonghua Kou Qiang Yi Xue Za Zhi.* 2002;37:415-417.
258. Li SH, Shi HJ, Wu DH, et al. [Study of lingual arterial CT angiography and security of partial glossectomy in obstructive sleep apnea hypopnea syndrome]. *Zhonghua er bi yan hou tou*

jing wai ke za zhi = Chinese journal of otorhinolaryngology head and neck surgery. 2009;44:831-836.
259. Lieu JEC, Chalivendra V, Ead B. Pediatric quality of life in children with otolaryngologic disease: What inventories are available and what is still needed? *Current Opinion in Otolaryngology and Head and Neck Surgery.* 2014;22:506-520.
260. Lin C-, Liao Y-, Chen N-, Lo L-, Chen Y-. Three-dimensional computed tomography in obstructive sleep apneics treated by maxillomandibular advancement. *Laryngoscope.* 2011;121:1336-1347.
261. Liu Z, Ren Q, Wang B, Xue H, Tian J, Zhao J. [The evaluation of virtual endoscopy and fiberoptic endoscopy in the diagnosis of obstructive sleep apnea syndrome]. *Lin chuang er bi yan hou tou jing wai ke za zhi = Journal of clinical otorhinolaryngology, head, and neck surgery.* 2008;22:257-259.
262. Löck K. Advances in pneumology -- physicians's viewpoint. *MMW Fortschr Med.* 2004;146.
263. Looby JF, Schendel SA, Lorenz HP, Hopkins EM, Aizenbud D. Airway analysis: With bilateral distraction of the infant mandible. *J Craniofac Surg.* 2009;20:1341-1346.
264. Lowe AA, Fleetham JA, Adachi S, Ryan CF. Cephalometric and computed tomographic predictors of obstructive sleep apnea severity. *American Journal of Orthodontics and Dentofacial Orthopedics.* 1995;107:589-595.
265. Lowe AA, Gionhaku N, Takeuchi K, Fleetham JA. Three-dimensional CT reconstructions of tongue and airway in adult subjects with obstructive sleep apnea. *American Journal of Orthodontics and Dentofacial Orthopedics.* 1986;90:364-374.
266. Lucey AD, King AJC, Tetlow GA, et al. Measurement, reconstruction, and flow-field computation of the human pharynx with application to sleep apnea. *IEEE Transactions on Biomedical Engineering.* 2010;57:2535-2548.
267. Ludlow JB, Davies-Ludlow LE, Brooks SL, Howerton WB. Dosimetry of 3 CBCT devices for oral and maxillofacial radiology: CB mercuray, NewTom 3G and i-CAT. *Dentomaxillofacial Radiology.* 2006;35:219-226.
268. Lumeng JC, Chervin RD. Epidemiology of pediatric obstructive sleep apnea. *Proceedings of the American Thoracic Society.* 2008;5:242-252.
269. Lye KW, Waite PD, Meara D, Wang D. Quality of life evaluation of maxillomandibular advancement surgery for treatment of obstructive sleep apnea. *Journal of Oral and Maxillofacial Surgery.* 2008;66:968-972.
270. Mahrous Mohamed A, Al Bishri A, Haroun Mohamed A. Distraction osteogenesis as followed by CT scan in pierre robin sequence. *Journal of Cranio-Maxillofacial Surgery.* 2011;39:412-419.
271. Maitre B. Update in pneumology. *Revue de Medecine Interne.* 2001;22:812-818.
272. Major M, El-Hakim H, Witmans M, Major P, Flores-Mir C. Adenoid hypertrophy in pediatric sleep disordered breathing and craniofacial growth: The emerging role of dentistry. *Journal of Dental Sleep Medicine.* 2014;1:83-87.

273. Makino S, Handa H, Suzukawa K, et al. Obstructive sleep apnoea syndrome, plasma adiponectin levels, and insulin resistance. *Clin Endocrinol (Oxf).* 2006;64:12-19.
274. Makino S, Iwata M, Fujiwara M, Ike S, Tateyama H. A case of sleep apnea syndrome manifesting severe hypertension with high plasma norepinephrine levels. *Endocr J.* 2006;53:363-369.
275. Manrique Franco K, López-Mezquita Torres E, Sánchez García L, Aragón Valera C, Sanchez-Vilar Burdiel O. Superior vena cava syndrome due to intrathoracic goiter. *Endocrinologia y Nutricion.* 2011;58:90-92.
276. Marcus CL. Pathophysiology of childhood obstructive sleep apnea: Current concepts. *Respir Physiol.* 2000;119:143-154.
277. Marcus CL, Curtis S, Koerner CB, Joffe A, Serwint JR, Loughlin GM. Evaluation of pulmonary function and polysomnography in obese children and adolescents. *Pediatr Pulmonol.* 1996;21:176-183.
278. Marcus CL, Katz ES, Lutz J, Black CA, Galster P, Carson KA. Upper airway dynamic responses in children with the obstructive sleep apnea syndrome. *Pediatr Res.* 2005;57:99-107.
279. Mariën S, Schmelzer B. Velopharyngeal anatomy in snorers and patients with obstructive sleep apnea. *Acta Otorhinolaryngol Belg.* 2002;56:93-99.
280. Mattar SEM, Matsumoto MAN, Valera FCP, Anselmo-Lima WT, Faria G. The effect of adenoidectomy or adenotonsillectomy on occlusal features in mouthbreathing preschoolers. *Pediatr Dent.* 2012;34:108-112.
281. Matthews KD, Richter RW. Binswanger's disease: Its association with hypertension and obstructive sleep apnea. *J Okla State Med Assoc.* 2003;96:265-268; quiz 269.
282. Maurer JT, Stuck BA. Update on upper airway evaluation in obstructive sleep apnea. *HNO.* 2008;56:1089-1097.
283. Mayer P, Pépin J-, Bettega G, et al. Relationship between body mass index, age and upper airway measurements in snorers and sleep apnoea patients. *European Respiratory Journal.* 1996;9:1801-1809.
284. 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;15:63-69.
286. McDuffie C, Lian TS, Thibodeaux J. Follicular dendritic cell sarcoma of the tonsil: A case report and literature review. *Ear, Nose and Throat Journal.* 2007;86:234-235.
287. Mechanick JI, Kushner RF, Sugerman HJ, et al. American association of clinical endocrinologists, the obesity society, and american society for metabolic & bariatric surgery medical guidelines for clinical practice for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient. *Surgery for Obesity and Related Diseases.* 2008;4:S109-S184.
288. Mégevand C, Savoy J, Boudrama A, Meier D. Madelung disease and obstructive sleep apnea syndrome: Apropos of a case. *Schweizerische medizinische Wochenschrift.Supplementum.* 2000;116:123S-126S.

289. Metes A, Hoffstein V, Direnfeld V, Chapnik JS, Zamel N. Three-dimensional CT reconstruction and volume measurements of the pharyngeal airway before and after maxillofacial surgery in obstructive sleep apnea. *J Otolaryngol.* 1993;22:261-264.
290. Mihaescu M, Mylavarapu G, Gutmark EJ, Powell NB. Large eddy simulation of the pharyngeal airflow associated with obstructive sleep apnea syndrome at pre and post-surgical treatment. *J Biomech.* 2011;44:2221-2228.
291. Miles PG, Vig PS, Weyant RJ, Forrest TD, Rockette HE Jr. Craniofacial structure and obstructive sleep apnea syndrome-a qualitative analysis and meta-analysis of the literature. 1996; 109: 163-72. *Am J Orthod Dentofacial Orthop.* 1996;109:163-72.
292. Milkiewicz P, Olliff S, Johnson AP, Elias E. Obstructive sleep apnoea syndrome (OSAS) as a complication of carcinoid syndrome treated successfully by hepatic artery embolization. *European Journal of Gastroenterology and Hepatology.* 1997;9:217-220.
293. Miro Castillo N, Roca-Ribas Serda F, Quesada Martinez JL, Perello Scherdel E. Comparative morphological imaging study of the pharynx in patients with obstructive sleep apnea syndrome (OSAS), healthy snorers and controls. *Acta Otorrinolaringol Esp.* 1998;49:34-40.
294. Mitchell RB. Adenotonsillectomy for obstructive sleep apnea in children: Outcome evaluated by pre- and postoperative polysomnography. *Laryngoscope.* 2007;117:1844-1854.
295. Mitchell RB, Garetz S, Moore RH, et al. The use of clinical parameters to predict obstructive sleep apnea syndrome severity in children: The childhood adenotonsillectomy (CHAT) study randomized clinical trial. *JAMA Otolaryngology - Head and Neck Surgery.* 2015;141:130-136.
296. Mitchell RB, Kelly J. Quality of life after adenotonsillectomy for SDB in children. *Otolaryngology - Head and Neck Surgery.* 2005;133:569-572.
297. Mitchell RB, Kelly J, Call E, Yao N. Long-term changes in quality of life after surgery for pediatric obstructive sleep apnea. *Archives of Otolaryngology - Head and Neck Surgery.* 2004;130:409-412.
298. Miyoshi M, Maehara K, Tanaka H, et al. A case of obstructive sleep apnea syndrome due to a parapharyngeal space tumor. *Pract Otorhinolaryngol.* 2008;101:45-49.
299. Mohsenifar Z, Stein M, DeLilly J, Mahler ME, Mandelkern M, Williams AJ. Regional metabolic dependency in obstructive sleep apnea. *Am J Med Sci.* 1994;308:75-78.
300. Monini S, Malagola C, Villa MP, et al. Rapid maxillary expansion for the treatment of nasal obstruction in children younger than 12 years. *Archives of Otolaryngology - Head and Neck Surgery.* 2009;135:22-27.
301. Mora R, Salami A, Passali FM, et al. OSAS in children. *Int J Pediatr Otorhinolaryngol.* 2003;67:S229-S231.
302. Motoi N, Kishi K, Fujii T, Tsuboi E, Ohashi K, Yoshimura K. Multiple bronchioloalveolar carcinomas in acromegaly: A potential role of insulin-like growth factor I in carcinogenesis. *Lung Cancer.* 2006;54:247-253.

303. Movahed MR, Hepner A, Lizotte P, Milne N. Flattening of the interventricular septum (D-shaped left ventricle) in addition to high right ventricular tracer uptake and increased right ventricular volume found on gated SPECT studies strongly correlates with right ventricular overload. *Journal of Nuclear Cardiology.* 2005;12:428-434.
304. Müller R, Büttner P. A critical discussion of intraclass correlation coefficients. *Statistics in Medicine.* 1994;13:2465-2476.
305. Muto T, Takeda S, Kanazawa M, Yamazaki A, Fujiwara Y, Mizoguchi I. The effect of head posture on the pharyngeal airway space (PAS). *Int J Oral Maxillofac Surg.* 2002;31:579-583.
306. Naji P, Alsufyani N, Lagrave`re M. Reliability of anatomic structures as landmarks in three-dimensional cephalometric analysis using CBCT . *Angle Orthod.* 2014;86:000-000.
307. Nakagawa Y, Kishida K, Mazaki T, et al. Impact of sleep-disordered breathing, visceral fat accumulation and adiponectin levels in patients with night-time onset of acute coronary syndrome. *Am J Cardiol.* 2011;108:1266-1271.
308. Nakanishi-Minami T, Kishida K, Nakagawa Y, et al. Metabolic syndrome correlates intracoronary stenosis detected by multislice computed tomography in male subjects with sleep-disordered breathing. *Diabetology and Metabolic Syndrome.* 2012;4.
309. Nakata S, Noda A, Misawa H, Yanagi E, Yagi H, Nakashima T. Obstructive sleep apnoea associated with congenital choanal atresia. *J Laryngol Otol.* 2005;119:209-211.
310. Namyslowski G, Scierski W, Misiolek M, Urbaniec N, Lange D. Huge retropharyngeal lipoma causing obstructive sleep apnea: A case report. *European Archives of Oto-Rhino-Laryngology.* 2006;263:738-740.
311. Nandalike K, Shifteh K, Sin S, et al. Adenotonsillectomy in obese children with obstructive sleep apnea syndrome: Magnetic resonance imaging findings and considerations. *Sleep.* 2013;36:841-847.
312. Nastro Siniscalchi E, Gabriele G, Cascone P. Palatal fistula resulting from cocaine abuse: A case report. *Eur Rev Med Pharmacol Sci.* 2012;16:280-282.
313. Nayak KS, Fleck RJ. Seeing sleep: Dynamic imaging of upper airway collapse and collapsibility in children. *IEEE Pulse.* 2014;5:40-44. doi:10.1109/MPUL.2014.2339398; 10.1109/MPUL.2014.2339398.
314. Negahdar M, Zacarias A, Milam RA, Dunlap N, Woo SY, Amini AA. An automated landmark-based elastic registration technique for large deformation recovery from 4-d CT lung images. *Progress in Biomedical Optics and Imaging - Proceedings of SPIE.* 2012;8317 Accessed 19 December 2012.
315. Nixon GM, Kermack AS, Davis GM, Manoukian JJ, Brown KA, Brouillette RT. Planning adenotonsillectomy in children with obstructive sleep apnea: The role of overnight oximetry. *Pediatrics.* 2004;113:e19-25.
316. Nogueira RLM, Teixeira RC, Lima MC, Sant'ana E, Santos CF. Apnoea-hypopnoea and mandibular retrusion as uncommon findings associated with proteus syndrome. *Dentomaxillofacial Radiology.* 2007;36:367-371.

317. Nolan P. Chronic lymphatic leukaemia presenting as severe obstructive sleep apnoea. *Respirology.* 1996;1:299-301.
318. Offers E, Herbort C, Dumke K, Schneider H, Kolloch R. Rheumatoid arthritis complicated by pulmonary and myocardial involvement and obstructive sleep apnea syndrome. *Pneumologie.* 1996;50:906-911.
319. Ogawa T, Enciso R, Memon A, Mah J, Clark G. Evaluation of 3D airway imaging of obstructive sleep apnea with cone-beam computed tomography. *Stud Health Technol Inform.* 2005;111:365-368.
320. Ogawa T, Enciso R, Shintaku WH, Clark GT. Evaluation of cross-section airway configuration of obstructive sleep apnea. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2007;103:102-108.
321. Öğretmenoğlu O, Süslü AE, Yücel ÖT, Önerci TM, Şahin A. Body fat composition: A predictive factor for obstructive sleep apnea. *Laryngoscope.* 2005;115:1493-1498.
322. Olszewska E, Sieśkiewicz A, Rózycki J, Rogalewski M, Rogowski M, Tarasów E. Usefulness of cephalometric measurements in the diagnostics of patients with obstructive sleep apnea syndrome - preliminary report. *Otolaryngologia Polska.* 2007;61:95-101.
323. Olszewska E, Sieskiewicz A, Rozycki J, et al. A comparison of cephalometric analysis using radiographs and craniofacial computed tomography in patients with obstructive sleep apnea syndrome: Preliminary report. *European Archives of Oto-Rhino-Laryngology.* 2009;266:535-542.
324. Orea-Tejeda A, Valencia-Flores M, Castillo-Martinez L, et al. Abnormal SPECT myocardial perfusion imaging during periods of obstructive sleep apnea in morbid obese patients without known heart disease. *Revista de Investigacion Clinica.* 2003;55:18-25.
325. Osorio F, Perilla M, Doyle D, Palomo J. Cone beam computed tomography: An innovative tool for airway assessment. 2008;106:1803-1807. doi:10.1213/ane.0b013e318172fd03. *Anesth Analg.* 2008;106:1803-1807.
327. Pae EK, Lowe AA, Sasaki K, Price C, Tsuchiya M, Fleetham JA. A cephalometric and electromyographic study of upper airway structures in the upright and supine positions. *Am J Orthod Dentofacial Orthop.* 1994;106:52-59.
328. Palomo JM, Rao PS, Hans MG. Influence of CBCT exposure conditions on radiation dose. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology.* 2008;105:773-782. doi:DOI: 10.1016/j.tripleo.2007.12.019.
329. Papagrigorakis M, Vilos GA, Apostolidis C, Daskalopoulou E, Vlachogiannis M. Long-term surgical cure of severe obstructive sleep apnea in an adult patient with craniofacial dysostosis (crouzon's syndrome): A case report and literature review. *Sleep and Breathing.* 2011;15:239-248.
330. Paramasivan VK, Arumugam SV, Kameswaran M. Randomised comparative study of adenotonsillectomy by conventional and coblation method for children with obstructive sleep apnoea. *Int J Pediatr Otorhinolaryngol.* 2012.

331. Park S-, Yoon J-, Kim Y-, Hwang D-, Cho B-, Son W-. The evaluation of the nasal morphologic changes after bimaxillary surgery in skeletal class III maloccusion by using the superimposition of cone-beam computed tomography (CBCT) volumes. *Journal of Cranio-Maxillofacial Surgery.* 2012;40:e87-e92.
332. Paulson EP, Graham SM. Neurologic diagnosis and treatment in patients with computed tomography and nasal endoscopy negative facial pain. *Laryngoscope.* 2004;114:1992-1996.
333. Pearce MS, Salotti JA, Little MP, et al. Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: A retrospective cohort study. *The Lancet.* 2012;380:499-505.
334. Peh WCG, Ip MSM, Chu FSK, Chung K-. Computed tomographic cephalometric analysis of chinese patients with obstructive sleep apnoea. *Australas Radiol.* 2000;44:417-423.
335. Pelteret J-V, Reddy BD. Development of a computational biomechanical model of the human upper-airway soft-tissues toward simulating obstructive sleep apnea. *Clinical Anatomy.* 2014;27:182-200.
336. Pendlebury ST, Pépin J-, Veale D, Lévy P. Natural evolution of moderate sleep apnoea syndrome: Significant progression over a mean of 17 months. *Thorax.* 1997;52:872-878.
337. Pepin JL, Ferretti G, Levy P. Upper airway and sleep apnoea syndrome. *Rev Mal Respir.* 1995;12:441-451.
338. Pepin JL, Ferretti G, Veale D, et al. Somnofluoroscopy, computed tomography, and cephalometry in the assessment of the airway in obstructive sleep apnoea. *Thorax.* 1992;47:150-156.
339. Pépin JLD, Veale D, Ferretti GR, Mayer P, Levy PA. Obstructive sleep apnea syndrome: Hooked appearance of the soft palate in awake patients - cephalometric and CT findings. *Radiology.* 1999;210:163-170.
340. Perchet D, Fetita C, Prêteux F. Three-dimensional reconstruction of upper airways from MDCT. *Proceedings of SPIE - The International Society for Optical Engineering.* 2005;5672:212-223 Accessed 3 October 2013.
341. Peters P, Stark P, Essig Jr. G, et al. Lingual thyroid: An unusual and surgically curable cause of sleep apnoea in a male. *Sleep and Breathing.* 2010;14:377-380.
342. Pevernagie DA, Shepard Jr. JW. Effects of body position on upper airway size and shape in patients with obstructive sleep apnea. *Acta Psychiatr Belg.* 1994;94:101-103.
343. Pevernagie DA, Stanson AW, Sheedy II PF, Daniels BK, Shepard Jr. JW. Effects of body position on the upper airway of patients with obstructive sleep apnea. *American Journal of Respiratory and Critical Care Medicine.* 1995;152:179-185.
344. Pham D, Xu C, Prince J. Current methods in medical image segmentation. *annu rev biomed eng.* 2000;02:315-37.
345. Piccin O, Sorrenti G. Adult obstructive sleep apnea related to nasopharyngeal obstruction: A case of retropharyngeal lipoma and pathogenetic considerations. *Sleep and Breathing.* 2007;11:305-307.

346. Pillar G, Shehadeh N. Abdominal fat and sleep apnea: The chicken or the egg? *Diabetes Care.* 2008;31 Suppl 2:S303-309.
347. Pirila-Parkkinen K, Pirttiniemi P, Nieminen P, Tolonen U, Pelttari U, Löppönen H. Dental arch morphology in children with sleep-disordered breathing. *Eur J Orthod.* 2009;31:160-167.
348. Pirner S, Tingelhoff K, Wagner I, et al. CT-based manual segmentation and evaluation of paranasal sinuses. *European Archives of Oto-Rhino-Laryngology.* 2009;266:507-518.
349. Polo O, Brissaud L, Fraga J, Dejean Y, Billiard M. Partial upper airway obstruction in sleep after uvulopalatopharyngoplasty. *Archives of Otolaryngology - Head and Neck Surgery.* 1989;115:1350-1354.
350. Polo O, Tafti M, Fraga J, Billiard M. Pharyngeal CT studies in patients with mild or severe upper airway obstruction during sleep. *Sleep.* 1993;16:S152-S155.
351. Polo OJ, Tafti M, Fraga J, Porkka KVK, Dejean Y, Billiard M. Why don't all heavy snorers have obstructive sleep apnea? *Am Rev Respir Dis.* 1991;143:1288-1293.
352. Pontes-Neto OM, Fernandes RMF, Sander HH, et al. Obstructive sleep apnea is frequent in patients with hypertensive intracerebral hemorrhage and is related to perihematoma edema. *Cerebrovascular Diseases.* 2009;29:36-42.
353. Punjabi NM. The epidemiology of adult obstructive sleep apnea. *Proceedings of the American Thoracic Society.* 2008;5:136-143.
354. Purvin VA, Kawasaki A, Yee RD. Papilledema and obstructive sleep apnea syndrome. *Arch Ophthalmol.* 2000;118:1626-1630.
355. Qvist J, Hove HD, Welling K-K, Kreiborg S. Severe obstructive sleep apnea in a child with craniofacial anomaly. *Ugeskr Laeger.* 2004;166:2910-2912.
356. Rachmiel A, Aizenbud D, Pillar G, Srouji S, Peled M. Bilateral mandibular distraction for patients with compromised airway analyzed by three-dimensional CT. *Int J Oral Maxillofac Surg.* 2005;34:9-18.
357. Rachmiel A, Srouji S, Emodi O, Aizenbud D. Distraction osteogenesis for tracheostomy dependent children with severe micrognathia. *J Craniofac Surg.* 2012;23:459-463.
358. Rafailidis PI, Prapas SN, Kasiakou SK, Costeas XF, Falagas ME. Effusive-constrictive calcific pericarditis associated with streptococcus salivarius: Case report and review of the literature. *Cardiol Rev.* 2005;13:113-117.
359. Rama AN, Tekwani SH, Kushida CA. Sites of obstruction in obstructive sleep apnea. *Chest.* 2002;122:1139-1147.
360. Rama AN, Tekwani SH, Kushida CA. Sites of obstruction in obstructive sleep apnea. *Chest.* 2002;122:1139-1147.
361. Ramar K. Asymmetric tonsillar enlargement and obstructive sleep apnea. *Sleep Med.* 2008;9:209-210.
362. Rapoport DM, Garay SM, Goldring RM. Nasal CPAP in obstructive sleep apnea: Mechanisms of action. *Clinical Respiratory Physiology.* 1983;19:616-620.
363. Ravesloot MJ, de Vries N. One hundred consecutive patients undergoing drug-induced sleep endoscopy: Results and evaluation. *Laryngoscope.* 2011;121:2710-2716.

365. Reimão R, Papaiz EG, Papaiz LF. Pierre robin sequence and obstructive sleep apnea. *Arq Neuropsiquiatr.* 1994;52:554-559.
366. Remy-Jardin M, Faivre J-, Santangelo T, Tacelli N, Remy J. Imaging the heart-lung relationships during a chest computed tomography examination: Is electrocardiographic gating the only option? *J Thorac Imaging.* 2010;25:239-246.
367. Ren XB. CT studies on obstructive sleep apnea syndrome. *Zhonghua Jie He He Hu Xi Za Zhi.* 1992;15:103-105, 128.
368. Richards A, Quaghebeur G, Clift S, Holland A, Dahlitz M, Parkes D. The upper airway and sleep apnoea in the prader-willi syndrome. *Clin Otolaryngol.* 1994;19:193-197.
369. Ridgway EB, Ropper AE, Mulliken JB, Padwa BL, Goumnerova LC. Meningoencephalocele: A late complication of le fort III midfacial advancement in a patient with crouzon syndrome - case report. *Journal of Neurosurgery: Pediatrics.* 2010;6:368-371.
370. Riley R, Powell N, Guilleminault C. Cephalometric roentgenograms and computerized tomographic scans in obstructive sleep apnea. *Sleep.* 1986;9:514-515.
371. Román GC, Erkinjuntti T, Wallin A, Pantoni L, Chui HC. Subcortical ischaemic vascular dementia. *Lancet Neurology.* 2002;1:426-436.
372. Ronen O, Malhotra A, Pillar G. Influence of gender and age on upper-airway length during development. *Pediatrics.* 2007;120:e1028-e1034.
373. Rosenbluth KH, Kwiat DA, Harrison MR, Kezirian EJ. Hyoid bone advancement for improving airway patency: Cadaver study of a magnet-based system. *Otolaryngology - Head and Neck Surgery.* 2012;146:491-496.
374. Rosenfeld RM, Green RP. Tonsillectomy and adenoidectomy: Changing trends. *Annals of Otology, Rhinology and Laryngology.* 1990;99:187-191.
375. Ruan L-, Zhou S-, Wang S-. Palatine tonsil schwannoma: Correlation between clinicopathology and computed tomography features. *J Int Med Res.* 2008;36:1140-1147.
376. Rubinstein I, Zamel N, Hoffstein V. Dynamic upper airway narrowing in patients with obstructive sleep apnea. *AJR.American journal of roentgenology.* 1986;147:1330-1331.
377. Ryan CF, Lowe AA, Li D, Fleetham JA. Three-dimensional upper airway computed tomography in obstructive sleep apnea: A prospective study in patients treated by uvulopalatopharyngoplasty. *Am Rev Respir Dis.* 1991;144:428-432.
378. Sabour S. Prediction of 3-dimensional pharyngeal airway changes after orthognathic surgery: A methodological issue. *American Journal of Orthodontics and Dentofacial Orthopedics.* 2015;147:8.
379. Sakakibara H, Umemoto M, Kuwahara M, Suetsugu S. Treatment of obstructive sleep apnea syndrome with a mandibular positioning device and other nonsurgical modalities. *Nihon Kyōbu Shikkan Gakkai zasshi.* 1995;33 Suppl:76-84.
380. Sakkas GK, Gourgoulianis KI, Karatzaferi C, et al. Haemodialysis patients with sleep apnoea syndrome experience increased central adiposity and altered muscular composition and functionality. *Nephrology Dialysis Transplantation.* 2008;23:336-344.

381. Salah Z, Bartz D, Dammann F, Schwaderer E, Maassen MM, Straßer W. A fast and accurate approach for the segmentation of the paranasal sinus. *Informatik aktuell.* 2005:93-97 Accessed 9 October 2013.
382. Sam K, Lam B, Ooi CG, Cooke M, Ip MS. Effect of a non-adjustable oral appliance on upper airway morphology in obstructive sleep apnoea. *Respir Med.* 2006;100:897-902.
383. Sanna A, Fargnoli R, Camiciottoli G. Obstructive sleep apnea syndrome as a complication after tracheal surgery. *Journal of Clinical Sleep Medicine.* 2006;2:458-459.
384. Santamaria F, Andreucci MV, Parenti G, et al. Upper airway obstructive disease in mucopolysaccharidoses: Polysomnography, computed tomography and nasal endoscopy findings. *J Inherit Metab Dis.* 2007;30:743-749.
385. Santiago-Recuerda A, Gómez-Terreros FJ, Caballero P, et al. Relationship between the upper airway and obstructive sleep apnea-hypopnea syndrome in morbidly obese women. *Obesity Surg.* 2007;17:689-697.
386. SarIman N, Levent E, Çubuk R, Yurtlu Ş, Benli Aksungar F. Bronchial hyperreactivity and airway wall thickening in obstructive sleep apnea patients. *Sleep and Breathing.* 2011;15:341-350.
387. Saussez S, Mahillon V, Chantrain G, Thill MP, Lequeux T. Acromegaly presented as a cause of laryngeal dyspnea. *Auris Nasus Larynx.* 2007;34:541-543.
388. Sawka AM, Aniszewski JP, Young Jr. WF, Nippoldt TB, Yanez P, Ebersold MJ. Tension pneumocranium, a rare complication of transsphenoidal pituitary surgery: Mayo clinic experience 1976-1998. *J Clin Endocrinol Metab.* 1999;84:4731-4734.
389. Scarfe WC. Radiation risk in low-dose maxillofacial radiography. *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology.* 2012;114:277-280.
390. Schechter MS. Technical report: Diagnosis and management of childhood obstructive sleep apnea syndrome. *Pediatrics.* 2002;109.
391. Schechter MS. Technical report: Diagnosis and management of childhood obstructive sleep apnea syndrome. *Pediatrics.* 2002;109.
392. Schendel S, Powell N, Jacobson R. Maxillary, mandibular, and chin advancement: Treatment planning based on airway anatomy in obstructive sleep apnea. *Journal of Oral and Maxillofacial Surgery.* 2011;69:663-676.
393. Schendel SA, Hatcher D. Automated 3-dimensional airway analysis from cone-beam computed tomography data. *Journal of Oral and Maxillofacial Surgery.* 2010;68:696-701.
394. Schulz R, Fegbeutel C, Hackstein N, Seeger W. Obstructive sleep apnoea secondary to superior vena cava thrombosis in a patient with activated protein C resistance. *Somnologie.* 2002;6:173-175.
395. Schwab RJ. Imaging for the snoring and sleep apnea patient. *Dent Clin North Am.* 2001;45:759-796.
396. Schwab RJ. Upper airway imaging. *Clin Chest Med.* 1998;19:33-54.

397. Schwab RJ, Gefter WB, Hoffman EA, Gupta KB, Pack AI. Dynamic upper airway imaging during awake respiration in normal subjects and patients with sleep disordered breathing. *Am Rev Respir Dis.* 1993;148:1385-1400.
398. Schwab RJ, Goldberg AN. Upper airway assessment: Radiographic and other imaging techniques. *Otolaryngol Clin North Am.* 1998;31:931-968.
399. Schwartz A, Patil S, Laffan A, Polotsky V, Schneider H, Smith P. Obesity and obstructive sleep apnea: Pathogenic mechanisms and therapeutic approaches. *Proc Am Thorac Soc.* 2008;5:185-192.
400. Segal Y, Malhotra A, Pillar G. Upper airway length may be associated with the severity of obstructive sleep apnea syndrome. *Sleep and Breathing.* 2008;12:311-316.
401. Senchenkov A, Werning JW, Staren ED. Radiographic assessment of the infiltrating retropharyngeal lipoma. *Otolaryngology - Head and Neck Surgery.* 2001;125:658-660.
402. Seo A, Chung SK, Lee J, Kim J-, Kim H. Semiautomatic segmentation of nasal airway based on collaborative environment. *Proceedings - 2010 International Symposium on Ubiquitous Virtual Reality, ISUVR 2010.* 2010:56-59 Accessed 30 January 2013.
403. Shakhov AA, Rabukhina NA, Nerobeev AI, Vasil'ev AI. X-ray upper airway changes in individuals suffering from obstructive respiratory disorders during sleep. *Vestn Rentgenol Radiol.* 2000:4-7.
404. Sharma S. Levels of evidence. *Evidence-Based Eye Care.* 1999;1:5-6.
405. Sharma S, Sharma P. A novel technique of skeletonization for feature extraction in cadastral maps
. *IJECSE.* 2012;1:1057-1061.
406. Shelton KE, Woodson H, Gay S, Suratt PM. Pharyngeal fat in obstructive sleep apnea. *Am Rev Respir Dis.* 1993;148:462-466.
407. Shen J, Qi J, Yin J-. Study of low dose and dynamic multi-slice CT about obstructive sleep apnea syndrome in sleeping. *Chinese Journal of Radiology.* 2006;40:713-717.
408. Shepard Jr. JW, Garrison M, Vas W. Upper airway distensibility and collapsibility in patients with obstructive sleep apnea. *Chest.* 1990;98:84-91.
409. Shepard Jr. JW, Gefter WB, Guilleminault C, et al. Evaluation of the upper airway in patients with obstructive sleep apnea. *Sleep.* 1991;14:361-371.
410. Shepard Jr. JW, Olsen KD. Uvulopalatopharyngoplasty for treatment of obstructive sleep apnea. *Mayo Clin Proc.* 1990;65:1260-1267.
411. Shepard Jr. JW, Pevernagie DA, Stanson AW, Daniels BK, Sheedy PF. Effects of changes in central venous pressure on upper airway size in patients with obstructive sleep apnea. *American Journal of Respiratory and Critical Care Medicine.* 1996;153:250-254.
412. Shepard Jr. JW, Stanson AW, Sheedy PF, Westbrook PR. Fast-CT evaluation of the upper airway during wakefulness in patients with obstructive sleep apnea. *Prog Clin Biol Res.* 1990;345:273-279; discussion 280.

413. Shepard Jr. JW, Thawley SE. Evaluation of the upper airway by computerized tomography in patients undergoing uvulopalatopharyngoplasty for obstructive sleep apnea. *Am Rev Respir Dis.* 1989;140:711-716.
414. Shi H, Scarfe W, Farman A. Upper airway segmentation and dimensions estimation from cone-beam CT image datasets. *Int J CARS.* 2006;1:177-186.
415. Shi H, Scarfe WC, Farman AG. Upper airway segmentation and dimensions estimation from cone-beam CT image datasets. *International Journal of Computer Assisted Radiology and Surgery.* 2006;1:177-186.
416. Shibata M, Nawa H, Kise Y, et al. Reproducibility of three-dimensional coordinate systems based on craniofacial landmarks: A tentative evaluation of four systems created on images obtained by cone-beam computed tomography with a large field of view. *Angle Orthod.* 2012;82:776-784.
417. Shigeta Y, Enciso R, Ogawa T, Clark GT. Changes in three dimensional simulation models of the airway which are due to increases in age or body mass index. *Stud Health Technol Inform.* 2008;132:460-462.
418. Shigeta Y, Enciso R, Ogawa T, Ikawa T, Clark GT. Cervical CT derived neck fat tissue distribution differences in japanese males and females and its effect on retroglossal and retropalatal airway volume. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontology.* 2008;106:275-284.
419. Shigeta Y, Enciso R, Ogawa T, Shintaku WH, Clark GT. Correlation between retroglossal airway size and body mass index in OSA and non-OSA patients using cone beam CT imaging. *Sleep and Breathing.* 2008;12:347-352.
420. Shigeta Y, Ogawa T, Ando E, Clark GT, Enciso R. Influence of tongue/mandible volume ratio on oropharyngeal airway in japanese male patients with obstructive sleep apnea. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontology.* 2011;111:239-243.
421. Shigeta Y, Ogawa T, Tomoko I, Clark GT, Enciso R. Soft palate length and upper airway relationship in OSA and non-OSA subjects. *Sleep and Breathing.* 2010;14:353-358.
422. Shigeta Y, Ogawa T, Venturin J, Nguyen M, Clark GT, Enciso R. Gender- and age-based differences in computerized tomographic measurements of the orophaynx. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontology.* 2008;106:563-570.
423. Shinohara E, Kihara S, Yamashita S, et al. Visceral fat accumulation as an important risk factor for obstructive sleep apnoea syndrome in obese subjects. *J Intern Med.* 1997;241:11-18.
424. Shpirer I, Copel L, Broide E, Elizur A. Continuous positive airway pressure improves sleep apnea associated fatty liver. *Lung.* 2010;188:301-307.
425. Singh GD, Keropian B, Pillar G. Effects of the full breath solution appliance for the treatment of obstructive sleep apnea: A preliminary study. *Cranio - Journal of Craniomandibular Practice.* 2009;27:109-117.
426. Singh GD, Wendling S, Chandrashekhar R. Midfacial development in adult obstructive sleep apnea. *Dent Today.* 2011;30:124-127.

427. Sittitavornwong S, Waite PD. Imaging the upper airway in patients with sleep disordered breathing. *Oral and Maxillofacial Surgery Clinics of North America.* 2009;21:389-402.
428. Sittitavornwong S, Waite PD, Shih AM, et al. Evaluation of obstructive sleep apnea syndrome by computational fluid dynamics. *Semin Orthod.* 2009;15:105-131.
429. Smith D, Neal J, Rumboldt Z, Boyd Gillespie M. Radiology quiz case 3. *Archives of Otolaryngology - Head and Neck Surgery.* 2005;131:75+78-79.
430. Smurra MV. Upper airway imaging in sleep apnoea syndrome: Clinical applications. *Monaldi Archives for Chest Disease.* 1998;53:520-523.
431. Sorajja D, Gami AS, Somers VK, Behrenbeck TR, Garcia-Touchard A, Lopez-Jimenez F. Independent association between obstructive sleep apnea and subclinical coronary artery disease. *Chest.* 2008;133:927-933.
432. Spencer DJ, Jones JE. Complications of adenotonsillectomy in patients younger than 3 years. *Archives of Otolaryngology - Head and Neck Surgery.* 2012;138:335-339.
433. Springate SD. The effect of sample size and bias on the reliability of estimates of error: A comparative study of dahlberg's formula. *The European Journal of Orthodontics.* 2011 doi:10.1093/ejo/cjr010.
434. Stanford W, Galvin J. Cine CT in obstructive sleep apnea. *Am J Roentgenol.* 1988;150:468.
435. Stark P, Aguilar Jr. EA, Robbins KT. The diagnosis of obstructive sleep apnoea (pickwickian syndrome). the value of CT. *Fortschritte auf den Gebiete der Rontgenstrahlen und der Nuklearmedizin.* 1984;140:46-47.
436. Stark P, Norbash A. Imaging of the trachea and upper airways in patients with chronic obstructive airway disease. *Radiol Clin North Am.* 1998;36:91-105.
437. Stauffer JL, White DP, Zwillich CW. Pulmonary function in obstructive sleep apnea. relationships to pharyngeal resistance and cross-sectional area. *Chest.* 1990;97:302-307.
438. Stauffer JL, Zwillich CW, Cadieux RJ, et al. Pharyngeal size and resistance in obstructive sleep apnea. *Am Rev Respir Dis.* 1987;136:623-627.
439. Stein MG, Gamsu G, De Geer G. Cine CT in obstructive sleep apnea. *Am J Roentgenol.* 1987;148:1069-1074.
440. Stiasny-Kolster K, Doerr Y, Möller JC, et al. Combination of 'idiopathic' REM sleep behaviour disorder and olfactory dysfunction as possible indicator for α-synucleinopathy demonstrated by dopamine transporter FP-CIT-SPECT. *Brain.* 2005;128:126-137.
441. Storey-Bishoff J, Noga M, Finlay WH. Deposition of micrometer-sized aerosol particles in infant nasal airway replicas. *J Aerosol Sci.* 2008;39:1055-1065.
442. Stratemann S, Huang JC, Maki K, Hatcher D, Miller AJ. Three-dimensional analysis of the airway with cone-beam computed tomography. *American Journal of Orthodontics and Dentofacial Orthopedics.* 2011;140:607-615.
443. Strauss RA, Burgoyne CC. Diagnostic imaging and sleep medicine. *Dent Clin North Am.* 2008;52:891-915.
445. Stuck BA, Maurer JT. The value of imaging studies in obstructive sleep apnea. *Somnologie.* 2009;13:144-153.

446. Stuck BA, Maurer JT. Airway evaluation in obstructive sleep apnea. *Sleep Medicine Reviews.* 2008;12:411-436.
447. Sullivan CE, Issa FG. Obstructive sleep apnea. *Clin Chest Med.* 1985;6:633-650.
448. Sundaram P, Joshi JM. Tracheobronchomegaly associated tracheomalacia: Analysis by sleep study. *Indian J Chest Dis Allied Sci.* 2004;46:47-49.
449. Sung S-, Jeong S-, Yu Y-, Hwang C-, Pae E-. Customized three-dimensional computational fluid dynamics simulation of the upper airway of obstructive sleep apnea. *Angle Orthod.* 2006;76:791-799.
450. Suratt PM, Dee P, Atkinson RL. Fluoroscopic and computed tomographic features of the pharyngeal airway in obstructive sleep apnea. *Am Rev Respir Dis.* 1983;127:487-492.
451. Sutherland K, Lee RWW, Phillips CL, et al. Effect of weight loss on upper airway size and facial fat in men with obstructive sleep apnoea. *Thorax.* 2011;66:797-803.
452. Tait AR, Voepel-Lewis T, Burke C, Kostrzewa A, Lewis I. Incidence and risk factors for perioperative adverse respiratory events in children who are obese. *Anesthesiology.* 2008;108:375-380.
453. Tajudeen BA, Lanson BG, Roehm PC. Glossal abscess as a complication of tongue-base suspension surgery. *Ear, Nose and Throat Journal.* 2011;90.
454. Tao X, Zhu F, Chen W, Zhu S. The application of virtual endoscopy with computed tomography in maxillofacial surgery. *Chin Med J.* 2003;116:679-681.
456. Tasker C, Crosby JH, Stradling JR. Evidence for persistence of upper airway narrowing during sleep, 12 years after adenotonsillectomy. *Arch Dis Child.* 2002;86:34-37.
457. Tauman R, Gulliver TE, Krishna J, et al. Persistence of obstructive sleep apnea syndrome in children after adenotonsillectomy. *J Pediatr.* 2006;149:803-808.
458. Thakkar K, Yao M. Diagnostic studies in obstructive sleep apnea. *Otolaryngol Clin North Am.* 2007;40:785-805.
459. Thevasagayam M, Rodger K, Cave D, Witmans M, El-Hakim H. Prevalence of laryngomalacia in children presenting with sleep-disordered breathing. *Laryngoscope.* 2010;120:1662-1666.
460. Thomas B, Flet JG, Shyam R, Kirk RC, Gennery AR, Spencer DA. Chronic respiratory complications in pediatric heart transplant recipients. *Journal of Heart and Lung Transplantation.* 2007;26:236-240.
461. Tingelhoff K, Moral AI, Kunkel ME, et al. Comparison between manual and semi-automatic segmentation of nasal cavity and paranasal sinuses from CT images. *Annual International Conference of the IEEE Engineering in Medicine and Biology - Proceedings.* 2007:5505-5508 Accessed 30 January 2013.
462. Tino G. Clinical year in review I: Lung cancer, interventional pulmonology, pediatric pulmonary disease, and pulmonary vascular disease. *Proceedings of the American Thoracic Society.* 2007;4:478-481.
463. Tipton WL, Metz P. Three dimensional computed technology--a new standard of care. *International journal of orthodontics (Milwaukee, Wis.).* 2008;19:15-21.

464. Togeiro SMGP, Chaves CM, Palombini L, Tufik S, Hora F, Nery LE. Evaluation of the upper airway in obstructive sleep apnoea. *Indian J Med Res.* 2010;131:230-235.
465. Tokuyasu H, Harada T, Touge H, et al. Primary pulmonary cryptococcosis with multiple infiltrative shadows complicated by obstructive sleep apnea syndrome. *Nihon Kokyūki Gakkai zasshi = the journal of the Japanese Respiratory Society.* 2009;47:548-552.
466. Trudo FJ, Gefter WB, Welch KC, Gupta KB, Maislin G, Schwab RJ. State-related changes in upper airway caliber and surrounding soft- tissue structures in normal subjects. *American Journal of Respiratory and Critical Care Medicine.* 1998;158:1259-1270.
467. Tschopp KP. Modification of the hörmann technique of hyoid suspension in obstructive sleep apnoea. *J Laryngol Otol.* 2007;121:491-493.
468. Tso HH, Lee JS, Huang JC, Maki K, Hatcher D, Miller AJ. Evaluation of the human airway using cone-beam computerized tomography. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontology.* 2009;108:768-776.
469. Tsuchiya M, Lowe AA, Pae EK, Fleetham JA. Obstructive sleep apnea subtypes by cluster analysis. *Am J Orthod Dentofacial Orthop.* 1992;101:533-542.
470. Tsuiki S, Almeida FR, Bhalla PS, Lowe AA, Fleetham JA. Supine-dependent changes in upper airway size in awake obstructive sleep apnea patients. *Sleep and Breathing.* 2003;7:43-50.
471. Tsuiki S, Almeida FR, Lowe AA, Su J, Fleetham JA. The interaction between changes in upright mandibular position and supine airway size in patients with obstructive sleep apnea. *American Journal of Orthodontics and Dentofacial Orthopedics.* 2005;128:504-512.
472. Tulek B, Kanat F, Yosunkaya S, Ceran S, Suerdem M. Pneumothorax as an initial manifestation of obstructive sleep apnea syndrome. *Sleep and Breathing.* 2010;14:249-251.
473. Tuncyurek O, Eyigor H, Ozkul A. What is the importance of radiology in obstructive sleep apnea? *J Craniofac Surg.* 2011;22:1971-1973.
474. Tweedie DJ, Bajaj Y, Ifeacho SN, et al. Peri-operative complications after adenotonsillectomy in a UK pediatric tertiary referral centre. *Int J Pediatr Otorhinolaryngol.* 2012.
475. Tysome JR, Saleh HA. Sphenochoanal polyp presenting with concomitant nasal polyps. *Ear, Nose and Throat Journal.* 2007;86:50-52.
476. Ursavaş A, Karadag M, Burgazlioglu B, et al. Relief from sleep apnea after radiation and chemotherapy. *Clinical Lung Cancer.* 2007;8:502-503.
477. Valiathan M, El H, Hans MG, Palomo MJ. Effects of extraction versus non-extraction treatment on oropharyngeal airway volume. *Angle Orthod.* 2010;80:1068-1074.
478. Van den Broek MJA, Arbues A-, Chalard F, et al. Chiari type I malformation causing central apnoeas in a 4-month-old boy. *European Journal of Paediatric Neurology.* 2009;13:463-465.
479. Van Holsbeke C, De Backer J, Vos W, et al. Anatomical and functional changes in the upper airways of sleep apnea patients due to mandibular repositioning: A large scale study. *J Biomech.* 2011;44:442-449.

480. Verse T, Pirsig W, Kroker B. Obstructive sleep apnea and nasal polyps. *Laryngorhinootologie.* 1998;77:150-152.
481. Vgontzas AN, Papanicolaou DA, Bixler EO, et al. Sleep apnea and daytime sleepiness and fatigue: Relation to visceral obesity, insulin resistance, and hypercytokinemia. *J Clin Endocrinol Metab.* 2000;85:1151-1158.
482. Viera AJ, Bond MM, Yates SW. Diagnosing night sweats. *Am Fam Physician.* 2003;67:1019-1024.
483. Vigg A, Vigg A, Vigg A. Obstructive sleep apnea in a referral population in india. *Sleep and Breathing.* 2003;7:177-184.
484. Villareal A, Hudgel D, Roth T. Improvement of obstructive sleep apnea after radiation therapy of vocal cord carcinoma. *Sleep Med.* 2007;9:96-97.
485. Viswanathan M, Ansari M, Berkman N, et al. Assessing the risk of bias of individual studies in systematic reviews of health care interventions. *Agency for Healthcare Research and Quality Methods Guide for Comparative Effectiveness Reviews.* 2012;AHRQ Publication No. 12-EHC047-EF.
486. Vos W, De Backer J, Devolder A, et al. Correlation between severity of sleep apnea and upper airway morphology based on advanced anatomical and functional imaging. *J Biomech.* 2007;40:2207-2213.
487. Vos WG, De Backer WA, Verhulst SL. Correlation between the severity of sleep apnea and upper airway morphology in pediatric and adult patients. *Current Opinion in Allergy and Clinical Immunology.* 2010;10:26-33.
488. Wang Y, Wang J, Liu Y, et al. Fluid-structure interaction modeling of upper airways before and after nasal surgery for obstructive sleep apnea. *International Journal for Numerical Methods in Biomedical Engineering.* 2012.
489. Weese-Mayer DE, Brouillette RT, Naidich TP, McLone DG, Hunt CE. Magnetic resonance imaging and computerized tomography in central hypoventilation. *Am Rev Respir Dis.* 1988;137:393-398.
490. Weissheimer A, Menezes LMD, Sameshima GT, Enciso R, Pham J, Grauer D. Imaging software accuracy for 3-dimensional analysis of the upper airway. *American Journal of Orthodontics and Dentofacial Orthopedics.* 2012;142:801-813.
491. Whittle A, Finch SP, Mortimore I, MacKay T, Douglas N. Use of home sleep studies for diagnosis of the sleep apnoea/hypopnoea syndrome. *Thorax.* 1997;52:1068-1073.
492. Wittenborn W, Panchal J, Marsh JL, Sekar KC, Gurley J. Neonatal distraction surgery for micrognathia reduces obstructive apnea and the need for tracheotomy. *J Craniofac Surg.* 2004;15:623-630.
493. Wootton DM, Luo H, Persak SC, et al. Computational fluid dynamics endpoints to characterize obstructive sleep apnea syndrome in children. *J Appl Physiol.* 2014;116:104-112.
494. Xiao Y, Chen X, Shi H, et al. Evaluation of airway obstruction at soft palate level in male patients with obstructive sleep apnea/hypopnea syndrome: Dynamic 3-dimensional CT imaging

of upper airway. *Journal of Huazhong University of Science and Technology - Medical Science.* 2011;31:413-418.
495. Xu H, Yu Z, Mu X. The assessment of midface distraction osteogenesis in treatment of upper airway obstruction. *J Craniofac Surg.* 2009;20:1876-1881.
496. Xu JK, Ye JY, Chang QL, Wang J, Wang XY, Ding X. [Correlation between upper airway soft tissue 3-D measurement and the severity of obstructive sleep apnea hypopnea syndrome]. *Zhonghua er bi yan hou tou jing wai ke za zhi = Chinese journal of otorhinolaryngology head and neck surgery.* 2010;45:387-392.
497. Ya L, Sun H, Wang X, Liu W. The significance of CT measurement of craniopharyngeal cavity in healthy person. *Lin Chuang Er Bi Yan Hou Ke Za Zhi.* 2002;16:670-671.
498. Yamashita S, Dohi T, Narui K, Momomura S-. Therapeutic efficacy of continuous positive airway pressure in obstructive sleep apnea patients with acute aortic dissection: A case report. *J Atheroscler Thromb.* 2010;17:999-1002.
499. Ye J, Liu H, Zhang G-, et al. Outcome of adenotonsillectomy for obstructive sleep apnea syndrome in children. *Annals of Otology, Rhinology and Laryngology.* 2010;119:506-513.
500. Yildirim N, Şahan M, Karslioğlu Y. Adenoid hypertrophy in adults: Clinical and morphological characteristics. *J Int Med Res.* 2008;36:157-162.
501. Yin S, Yi H, Lu W, et al. [Genioglossus advancement and hyoid suspension plus uvulopalatopharyngoplasty for severe OSAHS]. *Lin Chuang Er Bi Yan Hou Ke Za Zhi.* 2005;19:673-677.
502. Yoshida T, Matsuda H, Horiuchi C, et al. A case of osteochondroma of the atlas causing obstructive sleep apnea syndrome. *Acta Otolaryngol.* 2006;126:445-448.
503. Young T. Rationale, design, and findings from the wisconsin sleep cohort study: Toward understanding the total societal burden of sleep-disordered breathing. *Sleep Medicine Clinics.* 2009;4:37-46.
504. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med.* 1993;328:1230-1235.
505. Yu X, Fujimoto K, Urushibata K, Matsuzawa Y, Kubo K. Cephalometric analysis in obese and nonobese patients with obstructive sleep apnea syndrome. *Chest.* 2003;124:212-8.
506. Yu C-, Hsiao H-, Lee L-, et al. Computational fluid dynamic study on obstructive sleep apnea syndrome treated with maxillomandibular advancement. *J Craniofac Surg.* 2009;20:426-430.
507. Yu C-, Hsiao H-, Tseng T-, et al. Computational fluid dynamics study of the inspiratory upper airway and clinical severity of obstructive sleep apnea. *J Craniofac Surg.* 2012;23:401-405.
508. Yu KK, White DR, Weissler MC, Pillsbury HC. Nontraumatic atlantoaxial subluxation (grisel syndrome): A rare complication of otolaryngological procedures. *Laryngoscope.* 2003;113:1047-1049.

509. Yucel A, Unlu M, Haktanir A, Acar M, Fidan F. Evaluation of the upper airway cross-sectional area changes in different degrees of severity of obstructive sleep apnea syndrome: Cephalometric and dynamic CT study. *Am J Neuroradiol.* 2005;26:2624-2629.
510. Yushkevich PA, Piven J, Hazlett HC, et al. User-guided 3D active contour segmentation of anatomical structures: Significantly improved efficiency and reliability. *Neuroimage.* 2006;31:1116-1128. doi:DOI: 10.1016/j.neuroimage.2006.01.015.
511. Zandieh S, Katz ES. Retrograde lacrimal duct airflow during nasal positive pressure ventilation. *Journal of Clinical Sleep Medicine.* 2010;6:603-604.
512. Zettergren-Wijk L, Linder-Aronson S, Nordlander B, Ågren K, Svanborg E. Longitudinal effect on facial growth after tonsillectomy in children with obstructive sleep apnea. *World Journal of Orthodontics.* 2002;3:67-72.
513. Zettergren-Wijk L, Forsberg C-, Linder-Aronson S. Changes in dentofacial morphology after adeno-/tonsillectomy in young children with obstructive sleep apnoea - A 5-year follow-up study. *Eur J Orthod.* 2006;28:319-326.
514. Zhang L, Li S, Cai C. [Compare of CT scan of the nasopharynx in patients with obstructive sleep apnea-hypopnea syndrome and health]. *Lin chuang er bi yan hou tou jing wai ke za zhi = Journal of clinical otorhinolaryngology, head, and neck surgery.* 2010;24:746-749.
515. Zhou L, Wang X, Yi B, Ma L, Ni DF, Jin ZY. Upper airway morphologic changes in obstructive sleep apnea hypopnea syndrome patients before and after orthognathic surgery and distraction osteogenesis. *Zhonghua Kou Qiang Yi Xue Za Zhi.* 2007;42:195-198.
516. Zhou M, Jiang M, Cheng Y, et al. [Diagnosis of obstructive level in pharynx with obstructive sleep apnea hypopnea syndrome with multiple detector-row spiral CT]. *Lin chuang er bi yan hou tou jing wai ke za zhi = Journal of clinical otorhinolaryngology, head, and neck surgery.* 2008;22:600-602.
517. Zou KH, Tuncali K, Silverman SG. Correlation and simple linear regression. *Radiology.* 2003;227:617-622. doi:10.1148/.
518. Zucconi M, Weber G, Castronovo V, et al. Sleep and upper airway obstruction in children with achondroplasia. *J Pediatr.* 1996;129:743-749.

List of Abbreviations

2D, 3D: Two, three dimensional

AHI: Apnea-hypopnia index

ASCII: American Standard Code for Information Interchange

AT: Adenotonsillectomy

BMI: Body mass index

CAD: Computer aided diagnosis

CBCT: cone beam computed tomography

CFD: Computational fluid dynamics

CPAP: Continuous positive airway pressure

ENT: Ear nose and throat

FOV: Field of view

GERD: Gastroesophygeal reflux disease

ICC: Intra-class correlation

IEA: Intra-examiner agreement

kVp: kiloVoltage peak

LEDGES: Local Decomposition Gradient Segmentation

mA: milliAmpere

MDCT: Multi-detector computed tomography

MEs: Measurement errors

MinXarea: Minimum cross-sectional area

MMA: Maxillary-mandibular advancement

MRI: Magnetic resonance imaging

MSLT: Multiple sleep latency test

NP: Nasopharyngeal airway

NREM: Non-rapid eye movement

NS: Nasal airway

ODI: Oxygen desaturation index

OP: Oropharyngeal airway

OSA: Obstructive sleep apnea

OSA-18: Obstructive sleep apnea-18 quality of life questionnaire

OSAS: Obstructive sleep apnea syndrome

PM: Portable Monitoring

PO: Pulse oximetry

PSG: Ploysomnography

PSQ: Pediatric sleep questionnaire

QOL: Quality of life

REM: Rapid eye movement

RME: Rapid maxillary expansion

ROI: Region of interest

SaO2: Oxygen saturation

SDB: sleep disordered breathing

SDist: Shorest distance

SNR: Signal to noise ratio

SRBD: Sleep related breathing disorder

STL: Steriolithographic

List of Tables

List of Figures

Appendix A

Chapter 2.1: Search terminology used for other databases

All EBM Reviews

Keyword	Hits
1. airway.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw]	8976
2. Upper.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw]	12465
3. Nasal.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw]	7409
4. pharyn*.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw]	2353
5. 1 or 2 or 3 or 4	28333
6. segmentation.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw]	142
7. reconstruction.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw]	2171
8. algorithm.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw]	1850
9. three dimensional imaging.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw]	46
10. 6 or 7 or 8 or 9	4153
11. cone beam computed tomography.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw] or Computed tomography.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw]	243627
12. 5 and 10 and 11	15

Scopus:

Keyword	Hits
1. TITLE-ABS-KEY(airway OR upper OR nasal OR pharynx)	790315
2. TITLE-ABS-KEY(segmentation OR reconstruction OR algorithm OR three dimensional imaging)	91788
3. TITLE-ABS-KEY(cone beam computed tomography OR computed tomography)	3135
4. 1 and 2 and 3	69

Appendix A

Chapter 2.2: Search terminology used for other databases

Database								
Scopus				Medline			**EBM**	
	Keywords	#hits		Keywords	#hits		**Keywords**	**#hits**
1	**TITLE-ABS-KEY (obstructive sleep apnea)**	18,408		obstructive sleep apnea.mp. or exp Sleep Apnea, Obstructive/	13,324		**Obstructive sleep apnea.mp. [mp= ti, ab, tx, kw, ct, ot, sh, hw]**	**1,025**
2	**TITLE-ABS-KEY (sleep disordered breathing)**	4,794		sleep disordered breathing.mp. or exp Sleep Apnea Syndromes/	20,796		**sleep disordered breathing.mp. [mp= ti, ab, tx, kw, ct, ot, sh, hw]**	**225**
3	**1or2**	20,900		1or2	22,291		**1or2**	**1,178**
4	**TITLE-ABS-KEY (cone beam computed tomography)**	4,081		cone beam CT.mp. or exp Cone-Beam Computed Tomography	2,211		**cone beam computed tomography.mp. [mp= ti, ab, tx, kw, ct, ot, sh, hw]**	**37**
5	**TITLE-ABS-KEY (computed tomography)**	376,60		exp Tomography, X-Ray Computed/ or computed tomography.mp.	310,24		**Computed tomography.mp. [mp= ti, ab, tx, kw, ct, ot, sh, hw]**	**3,657**
6	**4 or 5**	376,60		4 or 5	310,35		**4 or 5**	**3,659**
7	**3 and 6**	**346**		**3 and 6**	**355**		**3 and 6**	**4**

Total 705 articles

Appendix B

Chapter 5.1: Supplemental material

Detailed steps for Consistent Level: Courtesy of Xinyao Sun and Dr. Irene Cheng from the Department of Computing Science, University of Alberta.

$$Real\ Positive - RP$$

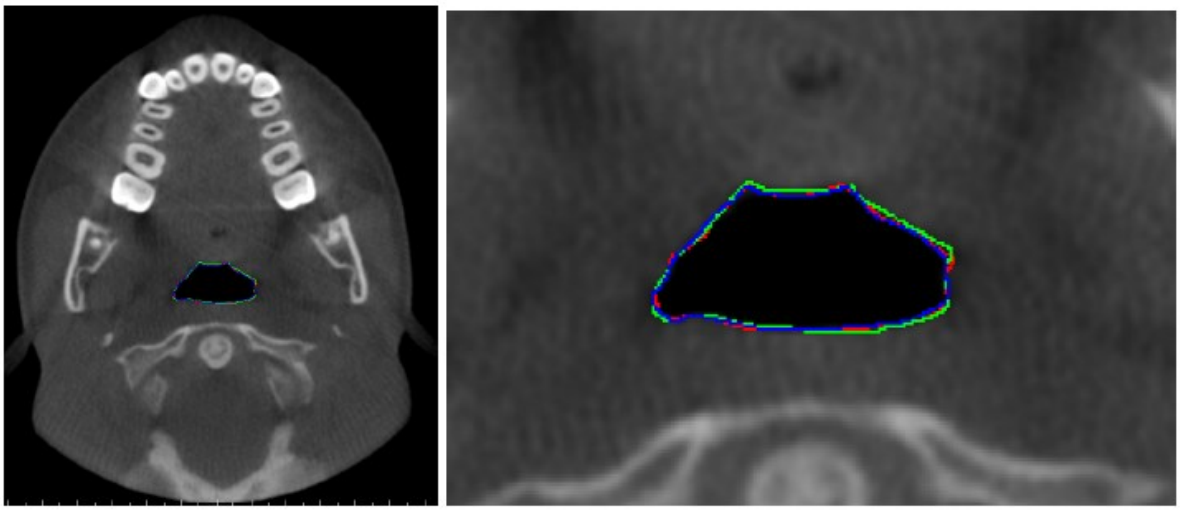
$$RP_{A\Rightarrow B} = \{P_A(x,y) : P_A \varepsilon A,\ \exists P_B \varepsilon B, SDist_B(P_A) \le 3\}$$
$$RP_{A\Rightarrow C} = \{P_A(x,y) : P_A \varepsilon A,\ \exists P_C \varepsilon C, SDist_C(P_A) \le 3\}$$

$$RP_{B\Rightarrow A} = \{P_B(x,y) : P_B \varepsilon B,\ \exists P_A \varepsilon A, SDist_A(P_B) \le 3\}$$
$$RP_{B\Rightarrow C} = \{P_B(x,y) : P_B \varepsilon B,\ \exists P_C \varepsilon C, SDist_C(P_B) \le 3\}$$

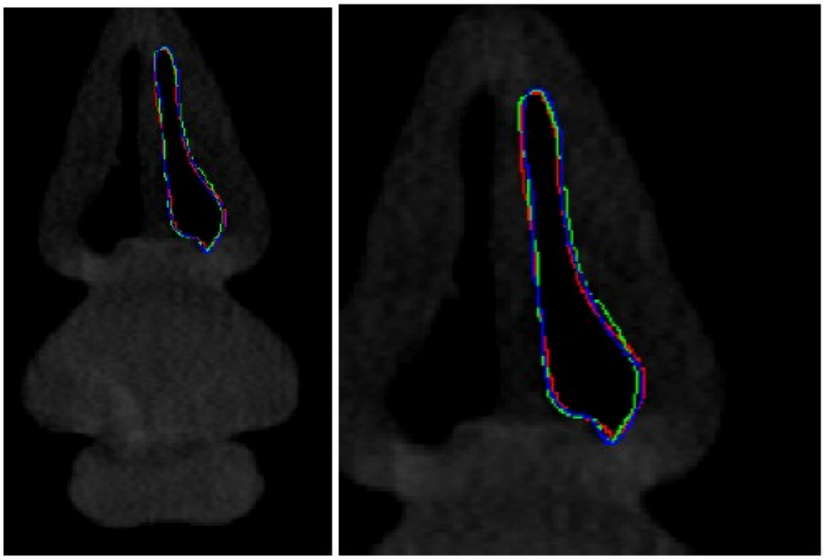
$$RP_{C\Rightarrow A} = \{P_C(x,y) : P_C \varepsilon C,\ \exists P_A \varepsilon A, SDist_A(P_C) \le 3\}$$
$$RP_{C\Rightarrow B} = \{P_C(x,y) : P_C \varepsilon C,\ \exists P_B \varepsilon B, SDist_B(P_C) \le 3\}$$

$$RP_A = RP_{A\Rightarrow B} \cap RP_{A\Rightarrow C}$$
$$RP_B = RP_{B\Rightarrow A} \cap RP_{B\Rightarrow C}$$
$$RP_C = RP_{C\Rightarrow A} \cap RP_{C\Rightarrow B}$$
$$RP = RP_A + RP_B + RP_C$$
$$\text{Consistent Level} = \frac{|RP|}{|A|+|B|+|C|}$$

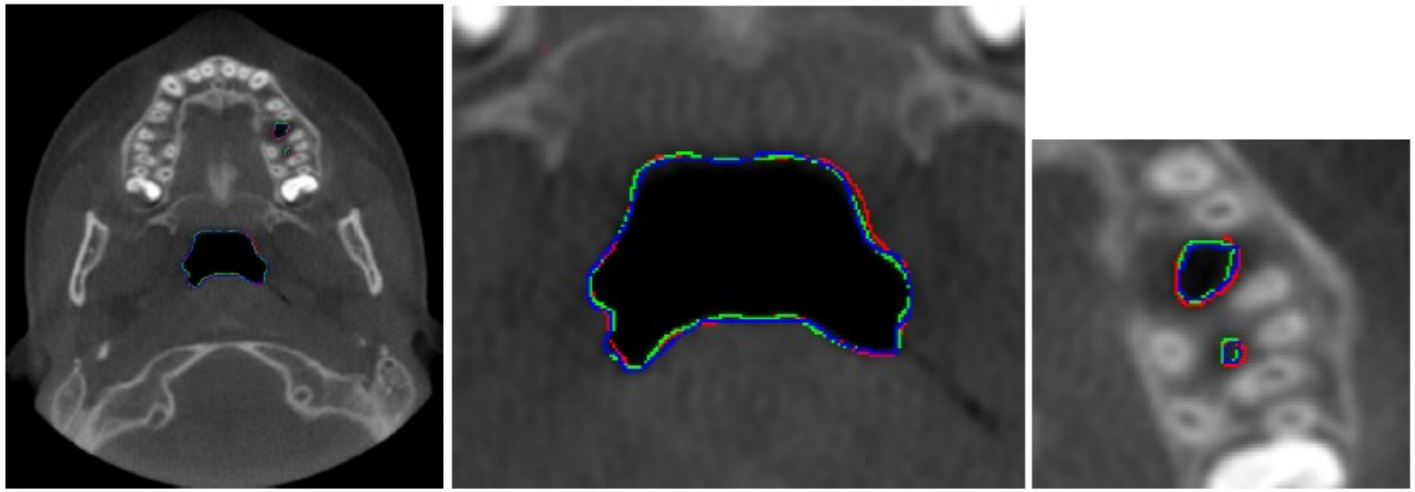
Chapter 5.1: Additional samples of tracing:



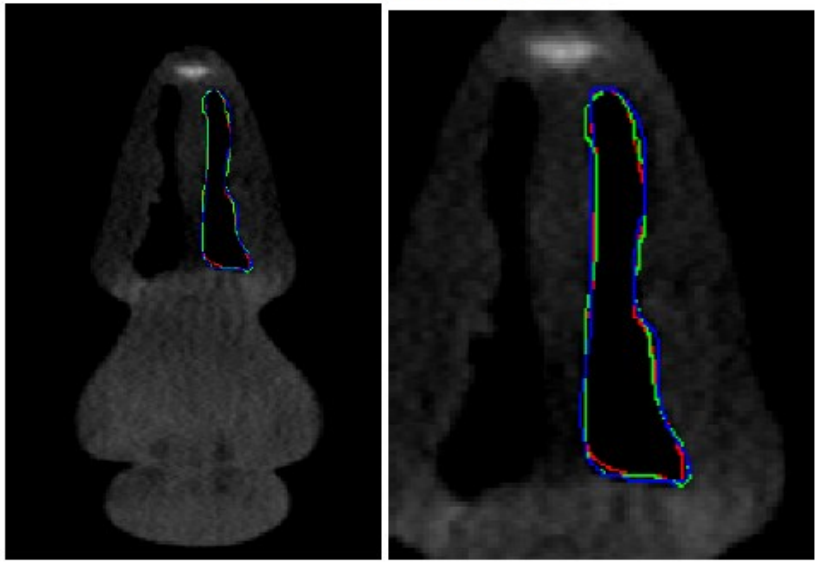
Case 2 Consistent Level:1



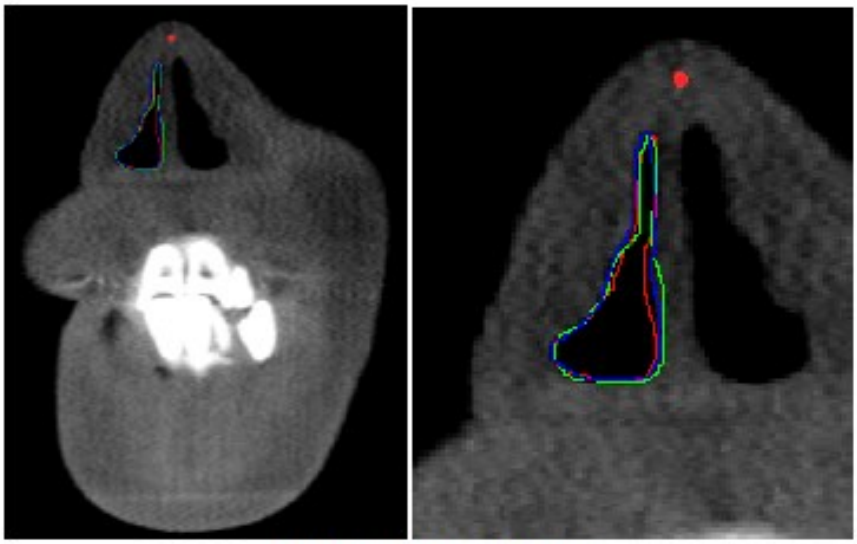
Case 3 Consistent Level:1



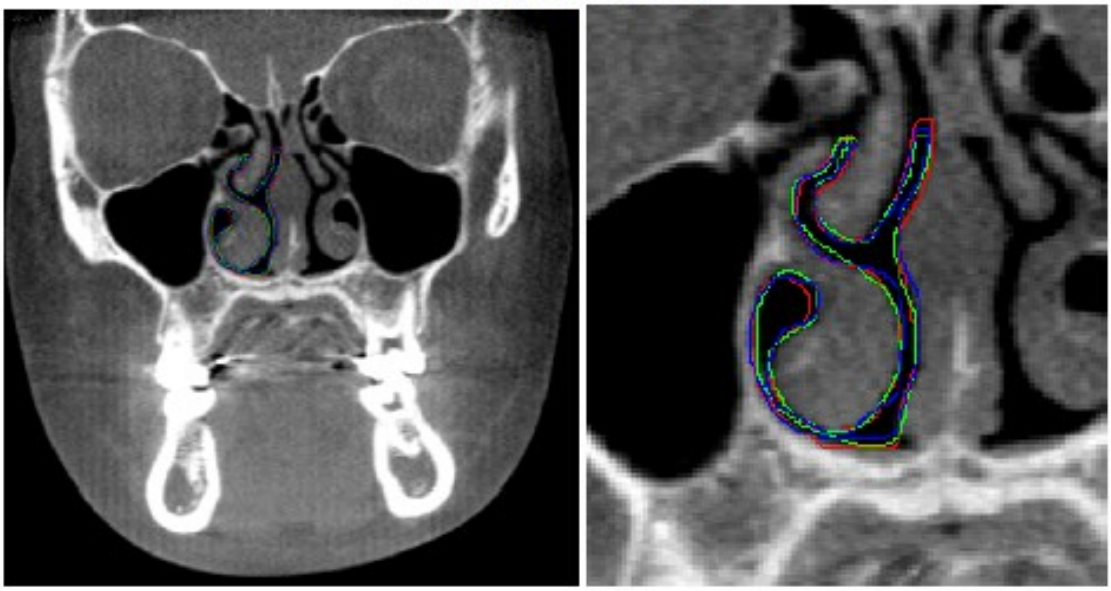
Case 4 Consistent Level:0.993



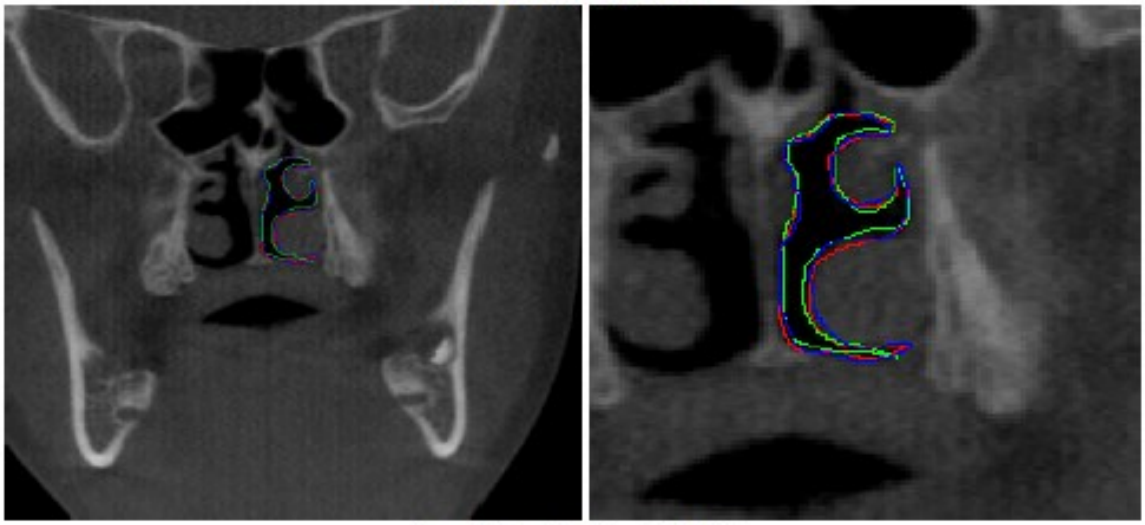
Case 5 Consistent Level:0.999



Case 7 Consistent Level:0.8971



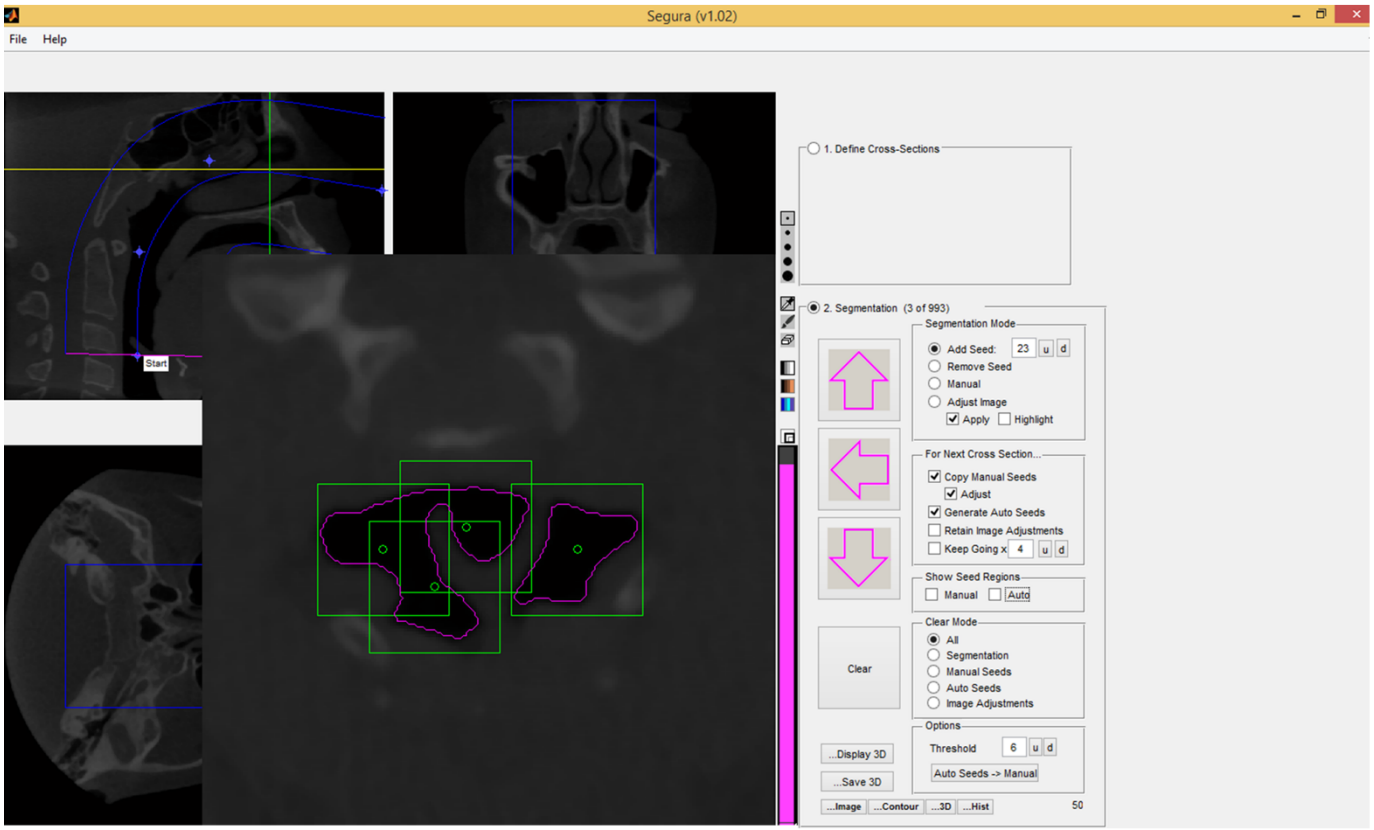
Case 8 Consistent Level:0.9



Case 9 Consistent Level:0.9006

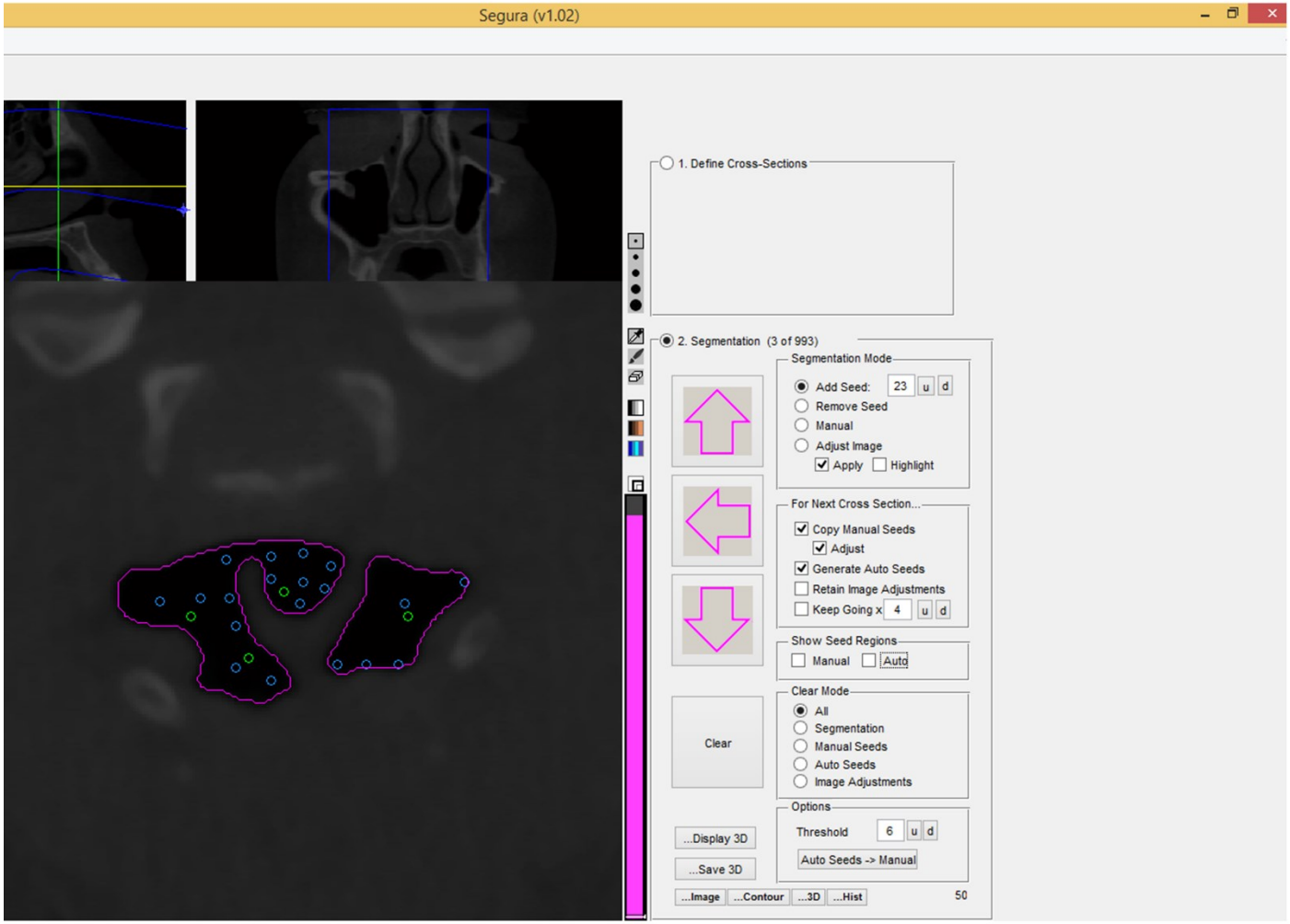
Appendix C

Chapter 5.3: Steps in Segura©

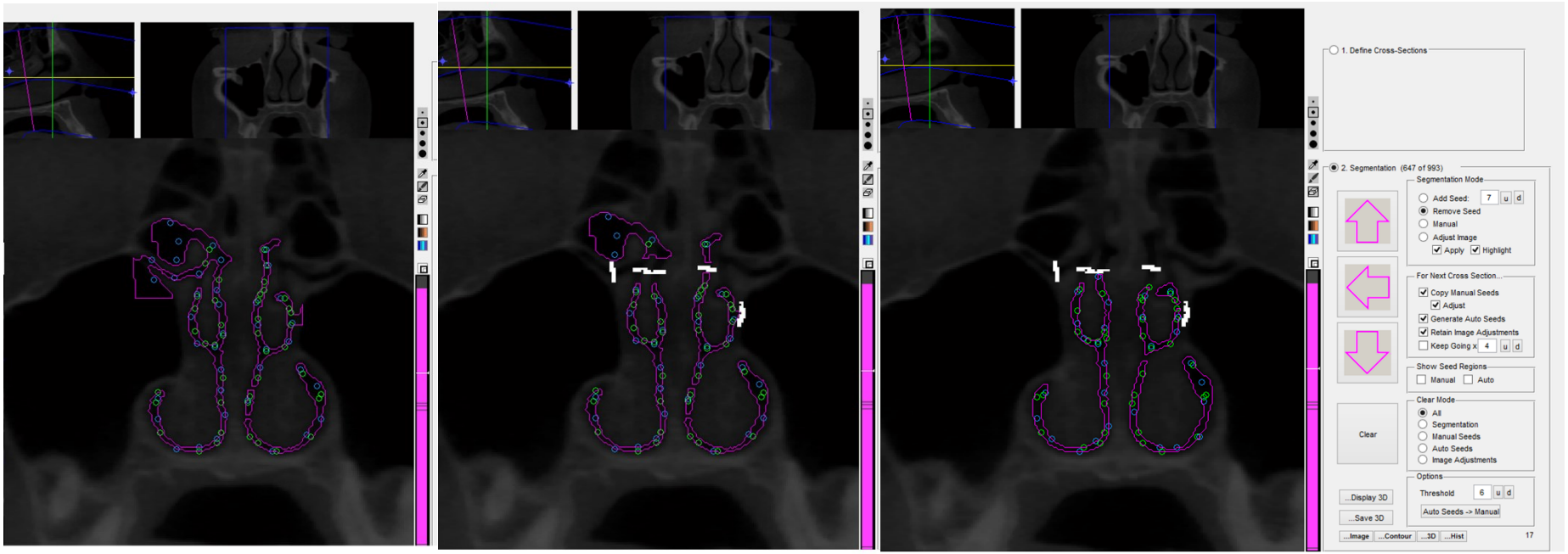


Layout of Segura©

- Area of interest (upper airway) is within the blue boundary.
- Horizontal pink line in the sagittal images mark the inferior boundary.
- Inset shows the first four seeds chosen by the operator, green squares mark the boundary of local threshold, and resultant segmentation marked in pink.
- The operator then presses the ⇧ button, the seeds will automatically copy to the following slices.



- The operator may choose to “Generate Auto Seeds”. These blue seeds will assess local thresholds similar the manual ones, green, selected at step 1.



As segmentation continues toward the nasal cavity, the seeds will detect airway in paranasal sinuses. The result is segmentation boundaries will "leak" into unwanted areas.

In this image, unwanted

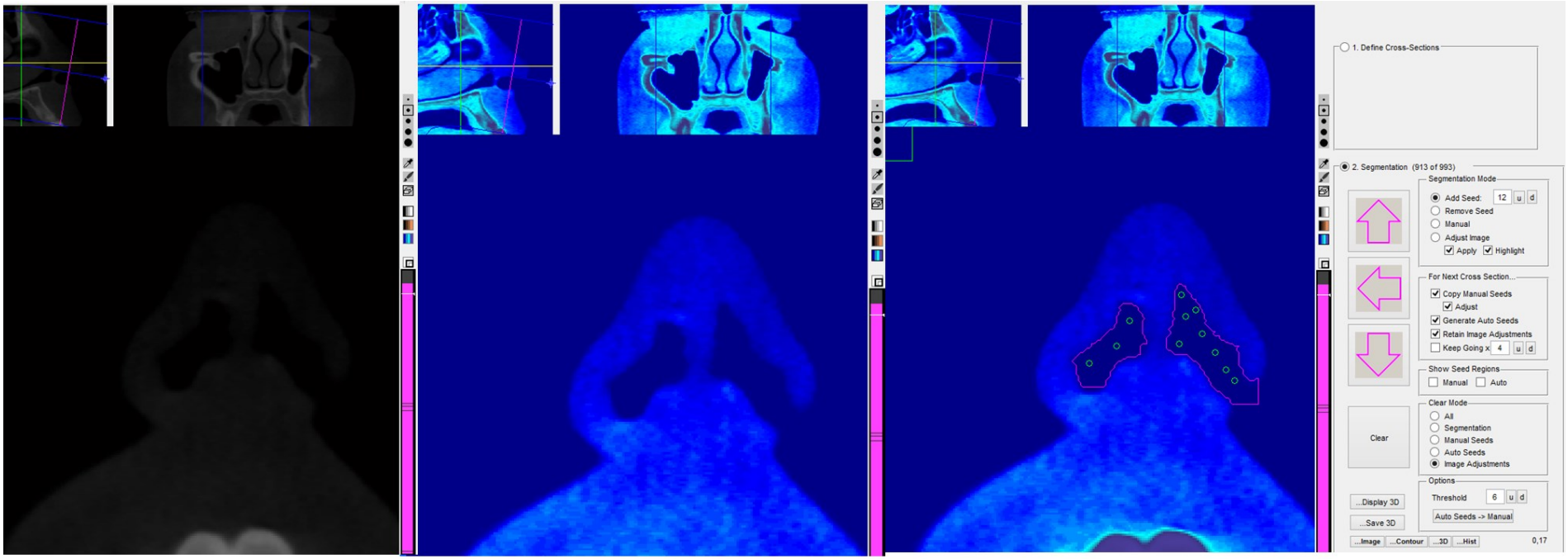
To avoid unwanted "leakage", the operator can choose to "seal" openings to paranasal sinuses by using the *Adjust Image* tool.

In this image, such openings are sealed, marked white.

Next, operator presses the ⇧ button.

The *Retain Image Adjustments* allows the tool to be effective as segmentation moves forward.

This prevented "leakage" of segmentation in the



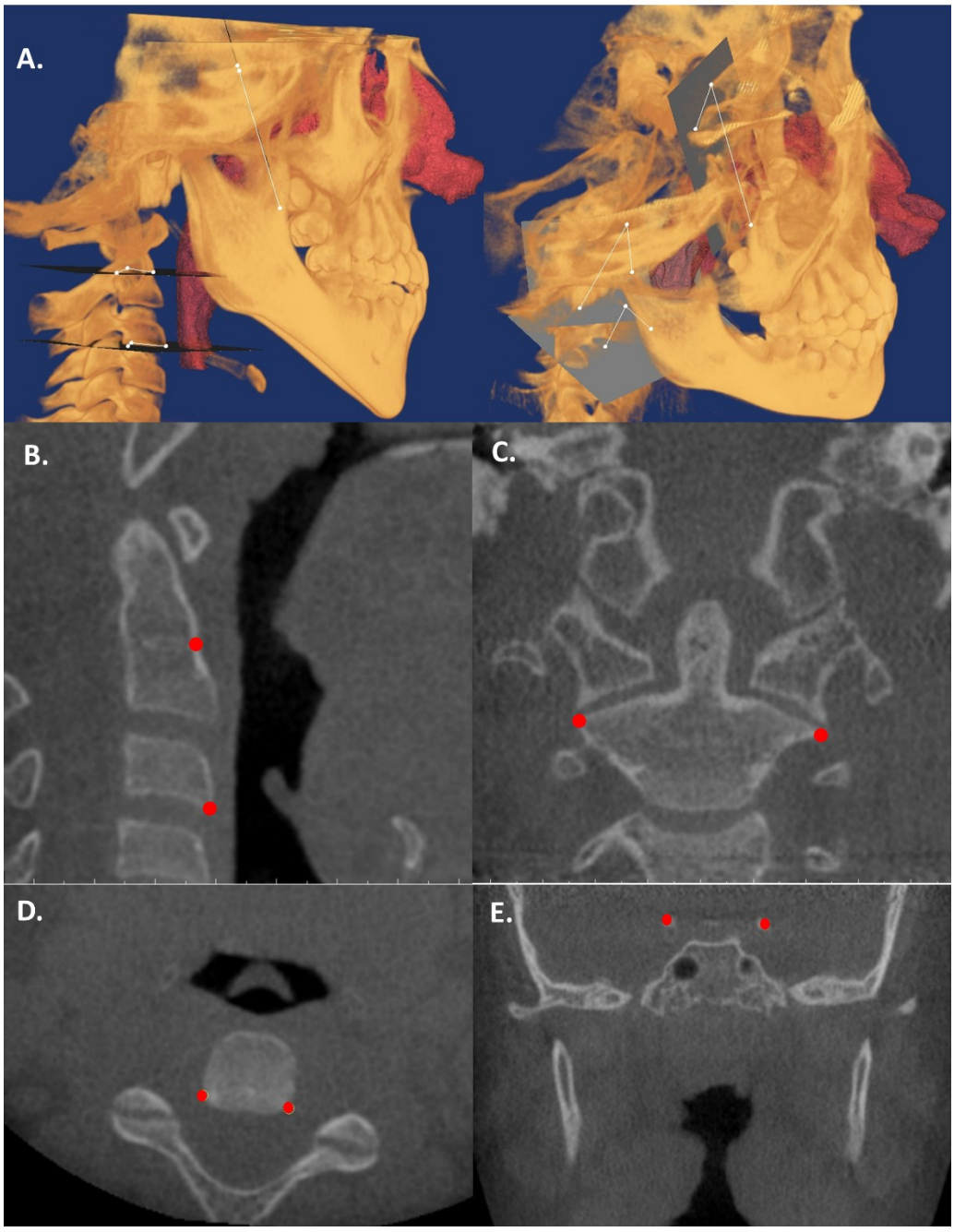
Towards the end of nose segmentation, airway definition in the anterior nares is challenging and difficult to visualized due to the small amount of radiation signal received in this region.

An option is selecting different tones of contrast to better highlight the airway space.

Due to the communication between the nasal airway and the exterior airway, segmentation is expected to "spill".

Two options exist:
Use the "seal" tool described previously, or
Simply add/erase segmentation using the *Manual* option.

Appendix D



Chapter 6 supplementary Figure: Three planes used to section the upper airway models. (A) 3D rendering of skull and airway showing the 3 planes. (B) Sagittal CBCT with anterior points of 2nd and 3rd planes: anterior-inferior base of odontoid and anterior-inferior body of C3. (C) Coronal CBCT with posterior points of 2nd plane: anterior-lateral points of C2 pedicles. (D) Axial CBCT with posterior points of 3rd plane: posterior-inferior-lateral points of body C3. (E) Coronal CBCT with posterior points of 1st plane: anterior clinoid processes.

Appendix E

Questionnaires used in Chapter 6 clinical pilot.

UNIVERSITY OF ALBERTA

Quality of life survey (OSA-18)

	None of the time	Hardly any of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time
Sleep disturbance							
During the past 4 weeks, how often has your child had...							
...loud snoring?	1	2	3	4	5	6	7
...breath-holding spells or pauses in breathing at night?	1	2	3	4	5	6	7
...choking or making gasping sounds while asleep?	1	2	3	4	5	6	7
..restless sleep or frequent awakening?	1	2	3	4	5	6	7
Physical symptoms							
During the past 4 weeks, how often has your child had...							
..mouth breathing because of nasal obstruction?	1	2	3	4	5	6	7
..frequent colds or upper respiratory infections?	1	2	3	4	5	6	7
..nasal discharge or runny nose?	1	2	3	4	5	6	7
..difficulty swallowing?	1	2	3	4	5	6	7
Emotional symptoms							
During the past 4 weeks, how often has your child had...							
..mood swings or temper tantrums?	1	2	3	4	5	6	7
..aggressive or hyperactive behavior?	1	2	3	4	5	6	7
..discipline problems?	1	2	3	4	5	6	7
Daytime function							
During the past 4 weeks, how often has your child had...							
..excessive daytime sleepiness?	1	2	3	4	5	6	7
..poor attention span or concentration?	1	2	3	4	5	6	7
..difficulty getting up in the morning?	1	2	3	4	5	6	7
Caregiver concerns							
During the past 4 weeks, how often have the problems above...							
..caused you to worry about your child's general health?	1	2	3	4	5	6	7
..created concern that your child is not getting enough air?	1	2	3	4	5	6	7
..interfered with your ability to perform daily activities?	1	2	3	4	5	6	7
..made you frustrated?	1	2	3	4	5	6	7

Pediatric Sleep Questionnaire

(Screening)

Name of the child:_____ Date of birth:_____

Person completing this form: _____

Date that you are completing the questionnaire: _____

Instructions: Please answer the questions about how your child **IN THE PAST MONTH**. Circle the correct response or *print* your answers in the space provided. "Y" means "yes," "N" means "no," and "DK" means "don't know." For this questionnaire, the word "usually" means "more than half the time" or "on more than half the nights."

Please answer the following questions as they pertain to your child <u>in the past month</u>.

		YES	NO	Don't Know
1.	**While sleeping, does your child:**			
	Snore more than half the time?	Y	N	DK
	Always snore?	Y	N	DK
	Snore loudly?	Y	N	DK
	Have "heavy" or loud breathing?	Y	N	DK
	Have trouble breathing, or struggle to breath?	Y	N	DK
2.	**Have you ever seen your child stop breathing during the night?**	Y	N	DK
3.	**Does your child:**			
	Tend to breathe through the mouth during the day?	Y	N	DK
	Have a dry mouth on waking up in the morning?	Y	N	DK
	Occasionally wet the bed?	Y	N	DK
4.	**Does your child:**			
	Wake up feeling unrefreshed in the morning?	Y	N	DK
	Have a problem with sleepiness during the day?	Y	N	DK
5.	**Has a teacher or other supervisor commented that your child appears sleepy during the day?**	Y	N	DK
6.	**Is it hard to wake your child up in the morning?**	Y	N	DK
7.	**Does your child wake up with headaches in the morning?**	Y	N	DK
8.	**Did your child stop growing at a normal rate at any time since birth?**	Y	N	DK
9.	**Is your child overweight?**	Y	N	DK
10.	**This child often:**			
	Does not seem to listen when spoken to directly.....	Y	N	DK
	Has difficulty organizing tasks and activities.....	Y	N	DK
	Is easily distracted by extraneous stimuli	Y	N	DK
	Fidgets with hands or feet, or squirms in seat	Y	N	DK
	Is "on the go" or often acts as if "driven by a motor"	Y	N	DK
	Interrupts or intrudes on others (eg butts into conversations or games)	Y	N	DK

Appendix F

Patient information Sheet, consent, and assent forms used in Chapter 6.

UNIVERSITY OF ALBERTA

INFORMATION SHEET & CONSENT

Title of Research Study: *Evaluation of treatment in children with sleep disordered breathing using CBCT.*

Principal Investigator(s): Dr. Paul Major Phone: 780.492.3312
Co-Investigator(s): Dr. Noura Alsufyani Phone: 780.492.1336

Dentistry and Dental Hygiene
Excellence in Dental Health

Purpose: To evaluate the size and shape of the upper airway (nose and throat) using Cone Beam Computed Tomography CBCT (3Dimentional orthodontic x-rays) before and after surgical treatment. We would like to better understand and explain the results of the treatment based on the shape of your child's airway.

Background: Your child has suspected breathing problems that may be caused by small sized or unfavorable shape of the upper airway. In order to properly diagnose these problems your child needs endoscopy, orthodontic x-rays, and the parent to answer few questionnaires. Airway endoscopy is a test that allows the doctor to look into your child's breathing passages (nose and all the way to the throat) using tiny telescopes to see how the airway behaves when the child is awake, asleep, or lightly sedated. For this study we would like your child to have 3D x-ray to allow proper measurements of your child's airway before and after treatment. The questionnaires will provide important information about his/her sleep and breathing. The endoscopy, 3D orthodontic x-rays and questionnaires are essential for proper diagnosis and needed even if you were not part of the study. The only procedure required especially for this study is to have 3D x-rays after treatment and quality of life questionnaires. Approximately 100 children with airway dysfunction (breathing problems) will take part in this study.

Procedures: If you agree to take part, your child will come to the Interdisciplinary Pediatric upper airway clinic one time for orthodontic x-rays and sleep questionnaires and to the hospital one time for nasoendoscopy on the same day. The questionnaires about your child's sleep and breathing will be completed by you, the parent/guardian. The information collected will be used to decide what treatment your child will require. A follow-up with the airway clinic will be scheduled within 6 months after surgery and a similar 3D orthodontic x-rays and quality of life sleep questionnaires will be completed. Everyone in the study will have the same procedures.

Benefits: The information collected will help us understand the results of your child's treatment, and may improve the way we prescribe and plan treatment in future patients.

Risks: Your child will not feel the x-ray. The test requires exposure to a small amount of radiation. This amount of radiation is very unlikely to lead to health problems in the future and is equal to 5 days of natural background radiation.The nasoendoscopy may feel uncomfortable, cause a momentary nosebleed, or hurt for a day or two. If your child's nose keeps hurting for more than 2 days or he/she has more nosebleeds, take your child to their doctor.

Withdrawal We need your participation in all aspects of the study (airway endoscopy, 3D x-rays, and questionnaires). All are necessary for us to properly examine your child's airway problem. You may choose to quit at any time without any adverse consequences. However, if you choose to quit **AFTER** your child diagnostic work-up or treatment (surgery), we will use any information collected.

Department of Dentistry
Faculty of Medicine and Dentistry
Dentistry/Pharmacy Centre • University of Alberta • Edmonton • Canada • T6G 2N8

Alternative Treatment: Your child does not have to join this study to receive treatment. If you choose not to be in this study, your child will be assessed by nasoendoscopy, sleep and breathing questionnaires, and 3D imaging prior to treatment (surgery) only; your child will not have 3D imaging AFTER treatment or quality of life questionnaire.

Confidentiality: During the study we will be collecting health data about your child. We will do everything we can to make sure that this data is kept private. No data relating to this study that includes your child's name will be released outside of the study doctor's office or published by the researchers. Sometimes, by law, we may have to release your information with your child's name so we cannot guarantee absolute privacy. However, we will make every legal effort to make sure that your child's health information is kept private.

Dentistry and Dental Hygiene
Excellence in Dental Health

The study doctor/study staff may need to look at your child's personal health records held at the study doctor's office, and/or kept by other health care providers that you may have seen in the past (i.e. your family doctor). Any personal health information that we get from these records will be only what is needed for the study.

During research studies it is important that the data we get is accurate. For this reason your health data, including your name, may be looked at by people from the University of Alberta or Health Research Ethics Board.

By signing this consent form you are giving permission for the study doctor/staff to collect, use and disclose information about you from your personal health records as described above. After the study is done, we will still need to securely store your health data that was collected as part of the study. At the University of Alberta, we keep data stored for 5 years after the end of the study.

Compensation for Injury: If your child becomes ill or injured as a result of being in this study, he/she will receive necessary medical treatment, at no additional cost to you. By signing this consent form you are not releasing the investigator(s), institution(s) and/or sponsor(s) from their legal and professional responsibilities.

Additional Contacts:
If you have questions regarding the study you can contact *Noura Alsufyani at alsufyan@ualberta.ca or Phone: 780.492.1336.* If you have questions regarding the study ethics or you want to express concerns regarding your rights as a study participant you can contact the University of Alberta Research Ethics Office at 780-492-2615. This office has no affiliation with the study investigators.

Department of Dentistry
Faculty of Medicine and Dentistry

Dentistry/Pharmacy Centre • University of Alberta • Edmonton • Canada • T6G 2N8

UNIVERSITY OF ALBERTA

CONSENT TO PARTICIPATION

Title of Study: *Evaluation of treatment in children with sleep disordered breathing using CBCT*

Principal Investigator: Dr. Paul Major Phone: 780.492.3312
Study Co-investigator: Dr. Noura Alsufyani Phone: 780.492.1336

Dentistry and Dental Hygiene
Excellence in Dental Health

	Yes	No
Do you understand that you and your child has been asked to be in a research study?	☐	☐
Have you read and received a copy of the attached Information Sheet?	☐	☐
Do you understand the benefits and risks involved in taking part in this research study?	☐	☐
Have you had an opportunity to ask questions and discuss this study?	☐	☐
Do you understand that you are free to leave the study at any time, without having to give a reason and without affecting your child's future medical care?	☐	☐
Has the issue of confidentiality been explained to you?	☐	☐
Do you understand who will have access to your records, including personally identifiable health information?	☐	☐
Do you want the investigator(s) to inform your family doctor that your child is participating in this research study? If so, give his/her name _____	☐	☐

Who explained this study to you? _____

I agree for my child and I to take part in this study,

_____
Signature of Parent/Guardian

(Printed Name) _____Date:_____

I believe that the person signing this form understands what is involved in the study and voluntarily agrees to participate.

Signature of Investigator or Designee _____ Date _____

A SIGNED COPY OF THIS INFORMATION AND CONSENT FORM MUST BE GIVEN TO THE RESEARCH PARTICIPANT

Department of Dentistry
Faculty of Medicine and Dentistry
Dentistry/Pharmacy Centre • University of Alberta • Edmonton • Canada • T6G 2N8

UNIVERSITY OF ALBERTA

Assent Form

Title of Research Study: *Evaluation of treatment in children with sleep disordered breathing using CBCT*

Principal Investigator: Dr. Paul Major Phone: 780.492.3312
Study Co-investigator: Dr. Noura Alsufyani Phone: 780.492.1336

You are being asked to be in this study because we suspect you have problems with your sleep or breathing and you may require treatment for your problem. We would like to better understand the results of your treatment.

What will I be asked to do? To help us have a better look at your upper airway (nose and throat), we need you to have an endoscopy (small camera inserted in your nose to see your nose and throat) and orthodontic 3D x-rays called Cone-beam computed tomography (CBCT). This will help us measure and study your airway before and after treatment. Also, you need to answer few questions about your sleep and breathing habits. We will ask you to come to our clinic for orthodontic x-ray's and airway endoscopy before treatment, then 3-6 months after your treatment for orthodontic x-ray's and quality of life questionnaire only. Everyone in the study will have the same procedures as you. The endoscopy, 3D orthodontic x-rays and questionnaires are essential for proper diagnosis and needed even if you were not part of the study. The only procedure required especially for this study is to have 3D x-rays after treatment and quality of life questionnaires. Around 100 children with airway problems will take part in this study.

Will it hurt? You will not feel the 3D x-ray. The airway endoscopy may feel uncomfortable, cause a short nose bleed, or hurt for a day or two. If your nose keeps hurting for more than 2 days or you have more nose bleeds, you must tell your mom, dad, or your doctor.

Will it help? The information we gather will help us understand your problems, and may help us in the future to better identify and solve similar problems in future patients.

Can I quit? Being part of this study is your choice. If you want to quit, that's ok. But we will still use any information we already gathered before you quit. If you wish to leave the study, please tell your mom or dad.

Who will know? No one except your parents and the doctor will know you're taking part in the study unless you want to tell them. Your name and your chart won't be seen by anyone except the doctors and nurses during the study. Any potential publication/presentation about this study will not identify you at all.

Your signature: We would like you to sign this form to show that you agree to take part. Your mom or dad will be asked to sign another form agreeing for you to take part in the study.

What if I have questions?
If you have any questions about the research now or later, please contact *Noura Alsufyani at alsufyan@ualberta.ca or Phone: 780.492.1336*

[ ] Yes, I will be in this research study. [ ] No, I don't want to do this.

Child's name	signature of child	date
Name of person obtaining assent	signature	date

Department of Dentistry
Faculty of Medicine and Dentistry

Appendix G: Health Research Ethics Board Approval Letters

Health Research Ethics Board

308 Campus Tower
University of Alberta, Edmonton, AB T6G 1K8
p. 780.492.9724 (Biomedical Panel)
p. 780.492.0302 (Health Panel)
p. 780.492.0459
p. 780.492.0839
f. 780.492.9429

Approval Form

Date:	January 22, 2013
Principal Investigator:	Paul Major
Study ID:	Pro00035567
Study Title:	Evaluation of surgical outcomes in children with sleep disordered breathing using Cone Beam computed tomography
Approval Expiry Date:	January 21, 2014

Approved Consent Documents:	Approval Date	Approved Document
	1/22/2013	Parent information and consent- clean

Funding/Sponsor: Full scholarship from the Saudi Cutural Bureau

Thank you for submitting the above study to the Health Research Ethics Board - Biomedical Panel. Your application has been reviewed and approved on behalf of the committee.

The following form part of this approval:
- Protocol, Version 1, 19 Dec 2012, with references; Informed Consent Form, Version 3, 22 Jan 2013; Assent Form, Version 3, 22 Jan 2013; Sleep Disturbances Scale for Children; Quality of Life Survey (osa-18); Child's Sleep Habits - Preschool and School-aged; and Pediatric Sleep Questionnaire.

The Health Research Ethics Board assessed all matters required by section 50(1)(a) of the Health Information Act. Subject consent for access to identifiable health information is required for the research described in the ethics application, and appropriate procedures for such consent have been approved by the HREB - Biomedical Panel. In order to comply with the Health Information Act, a copy of the approval form is being sent to the Office of the Information and Privacy Commissioner.

A renewal report must be submitted next year prior to the expiry of this approval if your study still requires ethics approval. If you do not renew on or before the renewal expiry date (January 21, 2014), you will have to re-submit an ethics application.

The membership of the Health Research Ethics Board - Biomedical Panel complies with the membership requirements for research ethics boards as defined in Division 5 of the Food and Drug Regulations and the Tri-Council Policy Statement. The HREB - Biomedical Panel carries out its functions in a manner consistent with Good Clinical Practices.

Approval by the Health Research Ethics Board does not encompass authorization to access the patients, staff or resources of Alberta Health Services or other local health care institutions for the purposes of the research. Enquiries regarding Alberta Health administrative approval, and operational approval for areas impacted by the research, should be directed to the Alberta Health Services Research Administration office, #1800 College Plaza, phone (780) 407-6041.

Sincerely,

J. Stephen Bamforth, MD
Associate Chair, HREB Biomedical

Note: This correspondence includes an electronic signature (validation and approval via an online system).

UNIVERSITY OF ALBERTA Alberta Health Services Covenant Health

Health Research Ethics Board

308 Campus Tower
University of Alberta, Edmonton, AB T6G 1K8
p. 780.492.9724 (Biomedical Panel)
p. 780.492.0302 (Health Panel)
p. 780.492.0459
p. 780.492.0839
f. 780.492.9429

Approval Form

Date:	March 16, 2011			
Principal Investigator:	Paul Major			
Study ID:	Pro00021181			
Study Title:	Automatic Segmentation of the Upper Airway using Cone Beam Computed Tomography: A validation study			
Approval Expiry Date:	March 14, 2012			
Sponsor/Funding Agency:	1/25/11	1/25/11	ID00002637	Full scholarship from the Saudi Cutural Bureau

Thank you for submitting the above study to the Health Research Ethics Board - Health Panel . Your application has been reviewed and approved on behalf of the committee.

The Research Ethics Board assessed all matters required by section 50(1)(a) of the Health Information Act. The REB Panel determined that the research described in the ethics application is a retrospective chart review for which subject consent for access to personally identifiable health information would not be reasonable, feasible or practical. Subject consent therefore is not required for access to the personally identifiable health information described in the ethics application.

In order to comply with the Health Information Act, a copy of the approval form is being sent to the Office of the Information and Privacy Commissioner.

A renewal report must be submitted next year prior to the expiry of this approval if your study still requires ethics approval. If you do not renew on or before the renewal expiry date, you will have to re-submit an ethics application.

Approval by the Health Research Ethics Board does not encompass authorization to access the patients, staff or resources of Alberta Health Services or other local health care institutions for the purposes of the research. Enquiries regarding Alberta Health Services administrative approval, and operational approval for areas impacted by the research, should be directed to the Alberta Health Services Regional Research Administration office, #1800 College Plaza, phone (780) 407-6041.

Sincerely,

Colleen Norris, Ph.D.
Associate Chair, Health Research Ethics Board - Health Panel

Note: This correspondence includes an electronic signature (validation and approval via an online system).

Health Research Ethics Board

308 Campus Tower
University of Alberta, Edmonton, AB T6G 1K8
p. 780.492.9724 (Biomedical Panel)
p. 780.492.0302 (Health Panel)
p. 780.492.0459
p. 780.492.0839
f. 780.492.9429

Approval Form - No HIA

Date:	September 4, 2012	
Principal Investigator:	Paul Major	
Study ID:	Pro00030422	
Study Title:	Topical contrast agents in the upper airway to improve signal to noise ratio in Cone Beam CT images: A Pilot study	
Approval Expiry Date:	September 3, 2013	
Approved Consent Document:	Approval Date 9/4/2012	Approved Document Patient information sheet and consent form

Funding/Sponsor: Full scholarship from the Saudi Cutural Bureau

Thank you for submitting the above study to the Health Research Ethics Board - Biomedical Panel. Your application has been reviewed and approved on behalf of the committee. The following form part of this approval:

- Protocol document, undated; Informed Consent Form, 15 Jun 2012; and Letter of invitation (advertisement), undated.

Note that the third page of the consent document is a blank page which should be removed. Please remove this blank page, which will result in the consent document being a total of 3 pages, however the version date of 15 Jun 2012 should be maintained.

A renewal report must be submitted next year prior to the expiry of this approval if your study still requires ethics approval. If you do not renew on or before the renewal expiry date (September 3, 2013), you will have to re-submit an ethics application.

The membership of the Health Research Ethics Board - Biomedical Panel complies with the membership requirements for research ethics boards as defined in Division 5 of the Food and Drug Regulations and the Tri-Council Policy Statement. The HREB - Biomedical Panel carries out its functions in a manner consistent with Good Clinical Practices.

Approval by the Health Research Ethics Board does not encompass authorization to access the patients, staff or resources of Alberta Health Services or other local health care institutions for the purposes of the research. Enquiries regarding Alberta Health administrative approval, and operational approval for areas impacted by the research, should be directed to the Alberta Health Services Research Administration office, #1800 College Plaza, phone (780) 407-6041.

Sincerely,

S.K.M. Kimber, MD, FRCPC
Chair, HREB Biomedical

Note: This correspondence includes an electronic signature (validation and approval via an online system).

UNIVERSITY OF ALBERTA Alberta Health Services Covenant Health

Health Research Ethics Board

308 Campus Tower
University of Alberta, Edmonton, AB T6G 1K8
p. 780.492.9724 (Biomedical Panel)
p. 780.492.0802 (Health Panel)
p. 780.492.0459
p. 780.492.0839
f. 780.492.9429

Approval

Date:	January 29, 2013
Study ID:	Pro00036840
Principal Investigator:	Manuel Lagravere Vich
Study Title:	Cone-beam computerized tomography registration for 3D airway analysis based on anatomical landmarks.
Approval Expiry Date:	January 28, 2014
Sponsor/Funding Agency:	Full scholarship from the Saudi Cutural Bureau

RSO-Managed Funding:

	Project ID	Project Title	Speed Code	Other Information
View	RES0009863	Automatic Segmentation Of The Upper Airway Using Cone Beam Computed Tomography: A Validation Study	48970	

Thank you for submitting the above study to the Health Research Ethics Board - Health Panel . Your application has been reviewed and approved on behalf of the committee.

The Health Research Ethics Board assessed all matters required by section 50(1)(a) of the Health Information Act. It has been determined that the research described in the ethics application is a secondary analysis of data collected under another research project for which subject consent for access to personally identifiable health information would not be reasonable, feasible or practical. Subject consent therefore is not required for access to personally identifiable health information described in the ethics application.

In order to comply with the Health Information Act, a copy of the approval form is being sent to the Office of the Information and Privacy Commissioner.

A renewal report must be submitted next year prior to the expiry of this approval if your study still requires ethics approval. If you do not renew on or before the renewal expiry date (January 28, 2014), you will have to re-submit an ethics application.

Approval by the Health Research Ethics Board does not encompass authorization to access the patients, staff or resources of Alberta Health Services or other local health care institutions for the purposes of the research. Enquiries regarding Alberta Health approvals should be directed to (780) 407-604. Enquiries regarding Covenant Health approvals should be directed to (780) 735-2274.

Sincerely,

Dr. Jana Rieger
Chair, Health Research Ethics Board - Health Panel

Note: This correspondence includes an electronic signature (validation and approval via an online system).