University of Alberta

Accuracy and Reliability of CBCT imaging for Assessing Adenoid Hypertrophy

by

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A thesis submitted to the Faculty of Graduate Studies and Research
in partial fulfillment of the requirements for the degree of

Master of Science

in

Medical Sciences - Orthodontics

Fall 2013
Edmonton, Alberta

Abstract

Purpose: evaluate 1) reliability and accuracy of cone-beam computed tomography (CBCT) for assessing adenoid size compared to nasoendoscopy (NE), 2) Influence of clinical experience on CBCT diagnosis.

Methods: Four blinded evaluators reviewed randomized CBCT images. Adenoid size was graded on a 4-point scale for CBCT and NE (by an pediatric otolaryngologist). Reliability was assessed with intra and inter-observer agreement. Accuracy was assessed with agreement between CBCT and NE, plus sensitivity / specificity analysis.

Results: 39 consecutively assessed, non-syndromic subjects (11.5 ± 2.8 years) were evaluated. CBCT demonstrated excellent sensitivity (88%) and specificity (93%), strong accuracy (ICC = 0.80, 95% CI ± 0.15), and very good reliability, both within observers (ICC = 0.85, 95% CI ± 0.08) and between observers (ICC = 0.84 ± 0.08). Clinical experience of the CBCT evaluators did not have a statistically significant effect.

Conclusions: CBCT is a reliable and accurate tool for identifying adenoid hypertrophy.

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List of Symbols, Nomenclature, or Abbreviations

3DO: 3-dimentional orthodontist – academic who's primary research is 3D imaging

A&T: adenotonsillectomy

AO: airway orthodontist – participates in multidisciplinary airway clinic

CBCT: cone-beam computed tomography

IAO: Intra-observer agreement

ICC: intra-class correlation coefficient

IEO: Inter-observer agreement

NE: nasoendoscopy

OMFR: oral maxillofacial radiologist

OSA: obstructive sleep apnea

PPO: private practice orthodontist

SDB: sleep disordered breathing

Chapter 1: Introduction

1.1 Anatomy, Epidemiology, and Relevance of Adenoid Hypertrophy

The adenoids are a collection of lymphatic tissue located in the most superior-posterior aspect of the nasopharynx. They are situated at the inflection point between the horizontally oriented nasal passage and the vertically oriented oropharynx. Being a lymphoid tissue, the adenoids play a role in immunity housing large numbers of immunocompetent cells such as B-cells, T-cells, lymphocytes, and macrophages.[1] As a result, the adenoids are highly prone to inflammation when an immune response is elicited against foreign antigens.[1]

Even in healthy children, a physiologic amount of adenoid enlargement is a part of normal craniofacial growth and development. The adenoid lymphoid tissue naturally increases to its largest size sometime between age 5-10, then continually decreases in size until adulthood.[2,3] Since children of this age range naturally have some element of relative lymph enlargement, any additional inflammation – actual inflamatory hypertrophy beyond physiologic adenoid enlargement – can easily introduce partial or complete nasopharyngeal obstruction.[4]

Epidemiologic studies have reported a high prevalence of adenoid hypertrophy in children. One large study of 1132 subjects observed a frequency a of 27% for children aged between five and seven, and 19-20% for children between the age of eight to fourteen.[5] Other smaller cross-sectional studies have observed frequencies of 37.9% among 370 children between three to nine years [6] and 57.7% among 213 children between the age six months to fifteen years[7].

When adenoid hypertrophy occurs in a chronic state there can be long periods of partial or complete impairment of nasal function,[8] which may lead to mouth breathing[6]. Chronic nasopharyngeal obstruction is believed to increase the risk for altered craniofacial growth, and increase the risk of pediatric sleep disordered breathing.

1.2 The Effect of Adenoid Hypertrophy

1.2.1 Adenoid Hypertrophy and Altered Cranio-facial Growth

Though a considerable number of previous researchers observed the relationship between nasal function and facial pattern, it was Linder-Aronson's seminal work that helped solidify the association between adenoid hypertrophy and altered human craniofacial growth. While he noted that adenoid obstruction occurred in all facial types, children with adenoid hypertrophy presented more frequently with a narrow maxillary dental arch, cross-bite, steep mandibular plane, and long anterior face height.[9] Such a craniofacial growth pattern was often termed "adenoid faces".

Linder-Aronson acknowledged that, in theory, a genetically driven facial pattern could cause the nasopharyngeal obstruction. However, he favored a hypothesis that nasopharyngeal obstruction – whether by adenoid hypertrophy or other etiology – increased resistance to nasal airflow such that children were obligated to mouth breathe; the resulting open mouth posture became the driving force behind altered craniofacial growth. He theorized that during mouth breathing, the tongue assumes a lower posture to facilitate oral airflow and therefore no longer rested in the palate to facilitate transverse development. Put simply: Linder-Aronson viewed maxillary transverse constriction and vertical growth pattern as a result of mouth breathing when there was collaborative evidence of nasopharyngeal obstruction.

While the patho-phsyiologic mechanism postulated by Linder-Aronson has been debated, the association between facial growth and nasal function has been repeatedly demonstrated.[10-13] A recent study has demonstrated that nasal obstruction due to deviated septum may cause the same altered craniofacial growth pattern as adenoid hypertrophy.[14] Even though a hyperdivergent craniofacial growth or dental crossbite can occur without airway obstruction, it is now almost universally accepted that nasopharyngeal obstruction can be a primary etiologic factor causing "adenoid faces".[15,16]

1.2.2 Adenoid Hypertrophy and Sleep Disordered Breathing

Sleep disordered breathing is a spectrum of disorders unified by respiratory disturbance or inadequate ventilation during sleep.[17] In this context, sleep disordered breathing can range from primary snoring to upper airway resistance syndrome to severe obstructive sleep apnea.[18] In the pediatric population, the frequency of obstructive sleep apnea is estimated at 1-5%[19], while the frequency of sleep disordered breathing (ex snoring) is estimated is estimated much higher ranging from 3% to 27%.[19] The consequences of sleep disordered breathing to overall health can be severe. Neurocognitive dysfunction including attention deficit, hyperactivity, reduced grades in school, and aggression[20,21]; cardiovascular dysfunction including hypertension[22], ventricular hypertrophy[23], valvular damage[24], or cor pulmonale[25]; and delayed growth [26] have all been reported.

Factors such as obesity[27,28], asthma,[29] ethnicity[30], former preterm birth[30], and environmental irritants[31] are all etiologic contributors and co-morbidities of pediatric sleep disordered breathing[1,32]. However, in the pediatric population, adenoid hypertrophy is the most pervasive primary etiology.[1-3,17,33]

1.3 The Effect of Adenoidectomy

1.3.1 Effect of Adenoidectomy on Craniofacial Growth

Linder-Aronson's work established a new level of firmness to the connection between adenoid hypertrophy and altered craniofacial growth. The next logical step was to investigate whether treating adenoid hypertrophy could normalize craniofacial growth.

Subsequent studies suggested a return to normal growth after adenoidectomy was possible. Multiple prospective, non-randomized clinical trials[34,35] demonstrated normalization of the mandibular plane angle (i.e. decrease in long face morphology) over the 5 year follow-up, but no noticeable change during the first year. Such a finding is not unexpected as growth takes time to occur. Though both studies demonstrated statistical significance, some trends were questionable and the clinical significance was not profound. These findings suggest that some normalization does occur, but growth pattern may not be fully restored to normal.

Current investigations have also produced mixed results. A recent prospective, non-randomized trial[5,36] evaluated growth in a pediatric population (n=34, mean age 5.6) with OSA for 5 years after adenotonsillectomy (A&T). Initially, the treatment group subjects had distinct facial morphology consistent with "adenoid faces" while control subjects did not. Five years after A&T, there was no discernable difference between the treatment and control groups. Conversely, a non-randomized prospective trial[37] evaluated growth differences between treated and untreated controls (n=80) after 1 year and found no difference. If the conclusions of Linder-Aronson's original intervention study[34] are valid, one year may not be sufficient time to observe a growth change, and Souki *et al*[37] may have incorrectly accepted the null hypothesis.

Unfortunately, none of the studies had strong methodological features, therefore inconsistencies between studies may be due to study biases (methodological flaws). Yet, the study that reported the strongest results[36] also treated the youngest subjects (mean age: 5.6 years). The other studies[34,35] reported subjects mean age 7.5 years and 8.2 years respectively. A recent cross-sectional study[13] suggested that children with obstructive adenoid hypertrophy should be treated before the age of six in order achieve total normalization of craniofacial growth. Therefore the spectrum of results across studies may be confounded by an unaccounted for age covariate. The clinical implication

might be: children with nasopharyngeal obstruction should be treated before age 6 for the best prognosis of normalized craniofacial growth.

1.3.2 Affect of Adenoidectomy on Pediatric Sleep Disordered Breathing

At the present time, A&T is the evidence-based, first line surgical treatment of pediatric obstructive sleep apnea.[17,32] One meta-analysis[38] described an average reduction of 13.9 AHI events following A&T and success rate of 82.9%, while another more recent systematic review estimated a success rate of only 66%.{Friedman:2009ds} However, the level of evidence generally is low, primarily coming from case series and cohort studies.[38,39]

Even though A&T is the current first surgical step, there are significant questions regarding its universal efficacy. Recent publications have reported failure rates of 49%[40] to 75%[41]. Continuous positive airway pressure (CPAP) has become the standard of care treatment for children with failed A&T. A growing body of research is suggesting that certain populations have a particularly poor prognosis following A&T. The presence of midface deficiency[42], obesity[28,43,44], family history of SBD[44], ethnicity,[44] asthma[43], GERD, septum deviation[45], and chronic rhinitis[45] all have various degrees of evidence to suggest a more guarded prognosis to A&T treatment.

Concurrent evidence is growing that alternative treatments are essential for SDB management, such as anti-inflammatory medication[46,47], proton-pump inhibitors[48], and orthodontics[45]. Unsurprisingly, each of these treatment alternatives addresses specific co-morbidities that may compromise the prognosis of A&T therapy.

In conclusion, recent evidence demonstrating a more guarded prognosis of A&T treatment for pediatric SDB suggests significant gaps in knowledge in current diagnostic standards. Further research is needed before clinicians can provide consistently

accurate, patient specific prognosis for A&T. Even though the role of A&T requires tailoring, its importance cannot be underestimated in SBD management. Because of the high prevalence of adenoid hypertrophy as a primary etiology in children with SDB, adenoitonsillectomy will always remain an important frontline surgical treatment option. Simply put, A&T should be seen as an initial, simple, and important treatment, but no longer viewed as a universal or ultimate surgical treatment for pediatric SDB.

1.4 Diagnosis of Adenoid Hypertrophy

Numerous tools are available to evaluate the nasal and nasopharyngeal airway. Clinical exam alone[49], acoustic rhinometry[8], lateral cephalometry[50], multi-row detector CT imaging[51], video fluoroscopy[52] have all been described as methods for evaluating nasopharyngeal patency. However, each of these methods has significant drawbacks. Clinical exam alone lacks the sensitivity to be useful[49]. Lateral cephalograms are fair, but tend to over-estimate adenoid size (see thesis section VIII: systematic review). Multi-row detector CT scans and video fluoroscopy are both very accurate, but require specialized equipment and exposes patients to unjustifiably high levels of radiation[51,52].

Beyond all other diagnostic methods, nasoendoscopy using a standardized grading system is the gold standard for diagnosis of adenoid hypertrophy.[53,54] Nasoendoscopy is minimally invasive, highly reliable, and easy for an otolaryngologist to perform. However, performing nasoendoscopy is outside the scope of practice for other health-care providers concerned with adenoid size – such as orthodontics or sleep medicine. While nasoendoscopy is an excellent diagnostic procedure, gaining access to an otolaryngologist is the most difficult step to getting a reliable diagnosis of adenoid hypertrophy.

1.5 Role of the Orthodontist in Airway Management

The orthodontist has several important roles in airway management. First, for patients with a history of nasopharyngeal obstruction and altered facial growth, orthodontic manipulation of the teeth and skeleton may help normalize the dento-facial appearance, thus improving the patient's esthetics. In this sense, an orthodontist's role may be to "clean up the mess".

Second, an orthodontist is well situated to play an important role in early detection and screening of certain children with airway dysfunction. Through timely diagnosis, an orthodontist may altogether prevent, or at least limit, the development of malocclusion and altered craniofacial growth. Using the same diagnostic skills, an orthodontist can screen for children with sleep disordered breathing. By facilitating timely referral to an otolaryngologist and / or sleep physician, and orthodontist can substantially improve a patients overall health and quality of life.

Third, through orthopedic manipulation of the facial skeleton, an orthodontist may be able to contribute to the treatment of select forms of sleep disordered breathing. Early research in rapid palatal expansion[45] and mandibular repositioning appliances are promising[55] and may yet become corner stone treatments for pediatric sleep disordered breathing. However, significant research is still required before an orthodontist can predictably treat sleep disordered breathing.

Therefore, at the present time an orthodontists most important role in airway management is to act as an early detector of airway dysfunction, and co-ordinate timely referral to appropriate physicians.

1.6 Statement of the Problem

Until recently, the orthodontist had two methods for evaluating a patient's airway: clinical exam, and 2D lateral cephalograms. Clinical exam alone has been demonstrated[49] as useful for ruling out disease (specificity =88%), but frequently misses patients who truly are airway compromised (sensitivity = 22%). 2D cephalometry is a key component of orthodontic diagnosis and treatment planning that can also be secondarily used for limited evaluation of adenoid size. A previous systematic review[56] could not identify any reliable method of evaluating adenoids on a 2D cephalogram, while a recent systematic review (see thesis section VIII: systematic review) demonstrated that cephalograms tend to over-estimate adenoid size. Orthodontists need an alternative, low risk, simple, and valid tool for evaluating the upper airway.

Advances in cone-beam computed tomography (CBCT) imaging have made 3D radiology more accurate, reliable, using lower radiation, and accessible to more orthodontists. CBCT imaging for orthodontic diagnosis and treatment planning has become an increasingly a common replacement for 2D imaging in many orthodontic practices. In theory, secondary evaluation of CBCT images that include the nasopharynx should yield very accurate images for evaluating potential adenoid obstructions. Despite the theoretical accuracy, the reliability CBCT imaging has never been quantified for evaluating adenoid size.

1.7 Null Hypothesis

The primary purpose of this study was to assess the accuracy and reliability of CBCT imaging for evaluating adenoid size by comparing the adenoid diagnosis with CBCT against nasoendoscopy. The null hypothesis was:

H_o: CBCT imaging is unable to accurately and reliably evaluate adenoid size

H_A: CBCT imaging is an accurate and reliable tool to screen for adenoid hypertrophy

In addition, a secondary objective was to assess whether clinical experience influences the accuracy and reliability of CBCT evaluations. The secondary null hypothesis was:

H_O: Clinical experience does not influence accuracy and reliability of CBCT interpretation

H_A: Clinical experience does influence accuracy and reliability of CBCT interpretation

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Chapter 2: Reliability of Diagnostic Tests for Adenoid Hypertrophy – a Systematic Review

2.1 Introduction

Adenoid hypertrophy is a common cause of impaired nasal airflow and nasopharyngeal obstruction.[1-3] Impaired nasal airflow may result in a spectrum of clinical problems ranging from mouth breathing[3,4] to sleep disordered breathing (SDB).[5,6] Both mouth breathing and SDB have been reported as a risk factors for growth and systemic health problems.

Mouth breathing has also been associated with altered craniofacial growth including: narrow maxillary arch, posterior crossbite, long anterior face height with clockwise mandibular growth rotation, anterior open bite and mandibular retrognathia.[7-11] SDB in children has been associated with numerous systemic health consequences including: reduced systemic growth,[12] systemic hypertension[13] and pulmonary hypertension[14] causing right or left ventricular hypertrophy respectively,[15, 16] or behavioural problems such as hyperactivity and attention deficit,[17] aggression,[17] and reduced grades in school[18]. With timely diagnosis and treatment most sequelae are potentially avoidable, or reversible.[19, 20]

Numerous tools to diagnose nasal obstruction have been reported including clinical history[21,22], rhinomanometry[23], acoustic rhinometry[24], lateral cephalometry[25, 26], fluoroscopy[27], computed tomography (CT)[28-30] and magnetic resonance imaging[31, 32]. However, nasoendoscopy (NE) is recognized as the reference standard for diagnosis of nasal and nasopharyngeal obstruction.[27,33-36]

The challenge facing the clinician is deciding which diagnostic modality provides the best information for the question posed for the affected individual at various levels of care. The choice of test may be affected by any of the following parameters: the portability of the test itself, access to testing, other indications of the test, skill set of the

clinician and benefit or harm to the patient as a result of the testing. The significant drawbacks with NE are invasiveness, patient discomfort and limited access to otolaryngologists for the scoping procedure, and even limited access to nasoendoscopic equipment for some otolaryngologists.[34] For these reasons alternative diagnostic methods are used in specific health care settings or by referring medical professionals. These professionals include commonly family physicians, pediatricians, dentists and orthodontists.

The objective is to systematically review the reliability (sensitivity and specificity) of alternative upper airway diagnostic tools against NE for establishing adenoid hypertrophy. The strengths, weaknesses, and clinical applicability of clinical examination, lateral cephalograms, video fluoroscopy, and CT imaging for diagnosis adenoid hypertrophy will be discussed. In addition, potential further research direction will be explored.

2.2 Methods

Protocol Registration: no registration of the systematic review protocol was submitted.

Information Sources & Search: PubMed, EMBASE, Web of Science, Pascal, and the Cochrane Library electronic databases were systematically searched from their inception to the second week of September, 2012. The search strategy was initially designed for PubMed (Table 2-1) and adapted to other databases. Where databases were able, electronic searches were limited to human studies and to children between 3-18 years old. The age limited was set as such because this range represents the clinically relevant range for a practicing orthodontist or referring general dentist. Hand searches through the bibliographies of relevant publications supplemented electronic searches in addition to grey literature searches with Google. No language restrictions were applied.

Eligibility Criteria:

- *Population*: children and adolescents with suspected nasal or nasopharyngeal airway obstruction
- *"Intervention"*: alternative diagnostic tool
- *Comparison*: reference standard diagnosis with nasoendoscopy
- *Outcome*: sensitivity / specificity analysis
- *Exclude*:
    - Subjects with syndromes (i.e. Down syndrome)
    - Atypical anatomy (i.e. cleft lip and palate)
    - Diagnosis of neoplasia in the upper airway area
    - History of trauma or upper airway surgery

Study Selection: Two reviewers independently evaluated titles and abstracts of potential publications evaluating any diagnostic test of the nasal and nasopharyngeal airway against NE. If the diagnostic field of view was obviously outside the upper airway (i.e. hypopharyngx, larynx, and lower airway), or subjects were adults (>18 years old), the papers were excluded. Publications passing phase 1 selection were retrieved in full. Two reviewers applied the remaining inclusion criteria to the full article in the second phase of selection (Figure 2-1). Disagreements were resolved with discussion until consensus was achieved.

Data Collection: Data was extracted in duplicate by two reviewers and compared for accuracy. Discrepancies were resolved by re-examining the literature as a team until consensus understanding was achieved.

Data Items: Diagnostic test being evaluated, reference diagnostic test, sample size, method of diagnostic interpretation, and sensitivity / specificity were the specific variables sought from each paper

Risk of Bias in Individual Studies: Methodology of selected articles were evaluated against a checklist (Table 2-2) derived from QAREL[37] and CONSORT[38]. All suggestions from QAREL were included in the present quality assessment. However, other methodology features not included in QAREL but deemed critical by the authors (prospective design, justified sample sizes, robust statistical reporting) were borrowed from CONSORT as could be applied to diagnostic studies.

Summary of Measures: Sensitivity and specificity of a diagnostic test for nasopharyngeal obstruction evaluated against NE as the reference standard.

Synthesis of Results: Data pooling for meta-analysis was not anticipated to be possible. Results of sensitivity and specificity analysis from individual studies were presented in Table 2-3.

Risk of Bias Across Studies: Because data pooling was not anticipated, evaluations such as I^2 heterogeneity, funnel plots, or sensitivity analysis could not be employed to evaluate bias across studies.

Additional Analysis: Raw data presented in Ysunza *et al*[27] was used to create a plot of lateral cephalogram airway evaluation against nasoendoscopy airway evaluation. (Figure 2-2)

Results

Study Selection: Searches of electronic databases, hand searches, and grey literature searches yielded 2552 articles. Of the 2552 titles, 51 articles were retrieved for further analysis. (Figure 2-1) In the end, a total of 7 articles met the inclusion criteria.

Study Characteristics: Of the 7 included articles, 4 were written in English, 2 in Spanish, and 1 in German. The reliability of structured clinical questionnaire (1/7), rhinomanometry (1/7) lateral cephalogram (4/7), video fluoroscopy (2/7), and multi-row detector CT (1/7) for diagnosing adenoid hypertrophy were identified. Absent from the literature were studies evaluating the reliability of rhinomanometry and MRI.

Risk of Bias: Quality of reported methodology was poor to good. (Table 2-2) Common weaknesses were: failure to fully blind evaluators (e.g. clinical findings or additional information that could identify a patient), failure to randomize the order of evaluation, no justification of sample sizes, no reported inter-observer reliability, and insufficient statistical reporting.

Synthesis of Results: Video fluoroscopy and CT imaging were found to be the best diagnostic tests, having both exceptional sensitivity and specificity (Table 2-3). Lateral skull films had consistently fair sensitivity around 65-75%, but the specificity varied widely depending on the method of evaluation used. Finally, clinical examination alone had poor sensitivity but high specificity (see Table 2-3 for all values).

Discussion

In patients with nasopharyngeal obstruction, it is important to have valid tools for evaluating common sites of obstruction, such as adenoids. NE is the currently accepted reference standard for evaluating adenoid size,[27,33-35] but requires both specialized equipment and access to an otolaryngologist. Because of the potential importance of early detection and intervention for nasal and naspharyngeal obstruction, a systematic review was carried out to assess the validity of various diagnostic techniques against NE.

Nasal and/or nasopharyngeal obstruction are common cause of airway dysfunction associated potential medical and craniofacial consequences. Early detection and intervention may play an essential role in an affected child's physical and psychosocial health.[7-18] A wide range of testing methods that are available for diagnosing adenoid hypertrophy with reasonable sensitivity and specificity, but none of these methods have been rigorously evaluated in large enough samples of children to be able to determine which tools are the best to use in which setting.

While the included studies provide significant insight to understanding imaging of the nasopharygeal airway, there is significant risk for evaluator bias (6 of 7 papers failing to randomize evaluation order, 5 of 7 papers failing to blind to patient info), and mild risk for selection bias (2 of 7 papers did not appear to have a representative sample). In addition, there is moderate potential for unaccounted confounding. The upper airway is dynamic soft tissue that can change substantially within days or even hours. Few studies (4 of 7) reportedly ensured the two diagnostic tests were run within a very short time of each other.

Clinical exam alone is insufficient to diagnose adenoid hypertrophy. Nasal obstruction index (NOI) demonstrated very low sensitivity (22%) but strong specificity (88%). The NOI index is a structured clinical exam that evaluates mouth breathing and speech hyponasality (while saying specific phrases) on a 4-point scale,[39] conditions that may be associated with more nasal and postnasal etiologies than just adenoid hypertrophy alone. Therefore NOI is reasonably good at identifying healthy individuals, but has very poor

sensitivity because it cannot differentiate between adenoid hypertrophy, rhinitis, rhinosinusitis deviated septum, nasal polyps, or other potential causes of upper airway obstruction.[1-3] In addition, NOI is a reasonably reliable method of evaluation; the original publication outlining NOI reported inter-observer agreement of κ=0.84-0.91.

Diagnosis of adenoid hypertrophy with video fluoroscopy and multi-row detector CT was in very strong agreement with the reference standard NE as seen in Table 2-3. Both tests had sensitivity, and specificity values greater than 90%. But despite the excellent reliability both tests are impractical for routine clinical use at most settings. First, video fluoroscopy and multi-row detector CT imaging require radiation, which most clinicians would consider unacceptable primarily for a screening procedure. Second, both video fluoroscopy and CT imaging require expensive and specialized equipment and skills that often is not readily accessible – even more so than nasoendoscopy.

Lateral cephalograms had moderate agreement with the gold standard NE. While the exact reliability score depended on the measurement method used for radiographic interpretation, sensitivity was generally between 65-75%. Specificity was far more variable ranging from 41% to 94%. Some of the variability in sensitivity / specificity can be attributed to the skill of the evaluator. Previous studies have reported fair to excellent intra-observer agreements for lateral head films, with values between κ=0.69 (95%CI 0.55-0.84) to 0.96 (95%CI 0.90-1.00).[40] Inter-observer agreement between an otolaryngologist and radiologist have been reported at 0.82 (95%CI 0.71-0.93).[40]

However, a theme emerged that went beyond the variability that rater skill could account for: studies that based the diagnosis more explicitly on adenoid size tended to have poorer specificity (adenoid size = 41%; subjective assessment of adenoid size 52%, 55%). Studies that based the diagnosis more explicitly on the size of the airway tended to have much better specificity (A/N ratio = 95%, airway-palate ratio = 96%, minimum airway space (McNamara's line) = 86%). These findings suggest that the most reliable method of assessing nasopharyngeal obstruction on a lateral cephalogram is by evaluating the size of the airway rather than the size of the adenoid.

Ysunza *et al*[27] were extremely helpful in understanding this dichotomy by providing all his raw data in the publication. A careful review of his data demonstrated that lateral head films were more likely to overestimate the adenoid size than underestimate it as seen in Figure 2-2. Knowing that a lateral cephalogram tends to overestimate adenoid size is very useful because it accurately explains both the high specificity but moderate sensitivity, and why evaluating airway patency is more reliable than evaluating adenoid size.

Therefore any clinician evaluating a lateral head film or cephalogram should do so understanding: 1) an apparently patent airway is quite likely accurate, but 2) an apparently obstructed airway may still be healthy. Consequently a diagnosis of adenoid obstruction on a lateral cephalogram alone is not an adequate basis to refer for an otolaryngology consultation. Only when combined with collaborative evidence – such a history significant for chronic allergies, snoring, unusual daytime drowsiness, delayed growth, attention deficit, or obesity[10, 17, 41] – should a referral be considered.

In summary, it is obvious that there is no perfect test. Nasoendoscopy remains the reference standard. With excellent diagnostic accuracy and low patient risk, nasoendoscopy is unlikely to ever be displaced as the reference standard. However access to otolaryngologists for diagnosis remains challenging. Every alternative to nasoendoscopy discussed in this review has drawbacks that are significant. Between lateral cephalographs combined with medical history and CBCT imaging, orthodontists can provide effective screening for patients requiring otolaryngology evaluation. Future research should focus on fine-tuning the diagnostic algorithms for orthodontists and quantifying the reliability of CBCT scans for secondary diagnosis adenoid hypertrophy.

2.5 Conclusions

- Video fluoroscopy and multi-row detector CT images have excellent reliability for diagnosing adenoid hypertrophy, but with significant radiation concerns
- Clinical exam alone can identify healthy patients, but cannot differentiate adenoid hypertrophy from any other cause of nasopharyngeal obstruction
- Lateral cephalograms have a tendency to over-estimate adenoid size, but are more reliable when the airway patency is evaluated.
- Significant need remains for the development of a reliable, clinically practical, readily accessible, and safe tools for screening adenoid hypertrophy

2.6 Tables

Table 2-1: Pubmed search strategy

Search group	Key word or MeSH term
1	((upper OR nasal OR nasopharyngeal) AND airway) OR adenoid* OR adenoid [MeSH] OR nasopharynx OR nasopharynx [MeSH] OR nasal obstruction [MeSH]
2	diagnostic OR diagnosis OR diagnosis [MeSH] OR assess* OR test OR evaluat* OR exam* OR investigat* OR rhinometry OR radiograph OR x-ray OR cephalomet* OR cephalometry [MeSH] OR fluoroscop* OR fluoroscopy [MeSH] OR tomography OR tomography, X-ray [MeSH] OR CT OR CBCT OR magnetic resonance OR MRI OR magnetic resonance imaging [MeSH]
3	endoscop* OR fiberoptic OR endoscopy [MeSH]
4	nasoendoscop*
5	1 AND 2
6	1 AND 3
7	4 OR 6
8	5 AND 7
Limits:	human, children & adolescents (under 18), NOT cancer

Table 2-2: Quality assessment of included studies

Study feature	Wormald [45]	Yzunza [27]	Torretta [46]	Barbosa [47]	Ysunza [48]	Hoppe [49]	Zicari [50]
Design							
Adequate study design	×	✓	✓	✓	✓	×	×
representative subjects	✓	✓	✓	×	✓	×	✓
sample size justified	×	✓	×	×	✓	×	×
representative evaluators	✓	✓	✓	✓	✓	✓	✓
blind to other evaluators	×	✓	only 1 rater	✓	✓	✓	×
blind to gold standard	✓	✓	×	✓	✓	✓	×
blind to clinical findings	✓	×	×	×	✓	✓	×
blind to pt info	×	×	×	×	✓	✓	×
evaluation order randomized	✓	×	×	×	×	×	×
Measurements							
stability of dx variable	×	×	✓	✓	×	×	×
correct use of dx tests	✓	✓	✓	✓	✓	✓	✓
intra-observer reliability	×	×	×	×	✓	×	×
inter-observer reliability	✓	✓	×	×	×	×	×
Statistical Analysis							
correct use of stats	✓	✓	✓	×	✓	×	✓
exact *P*-value stated	×	×	n/a	×	×	✓	✓
variance stated (95%CI or SD with n)	×	n/a	✓	×	n/a	✓	✓

✓ = reported × = not performed or not reported

Table 2-3: Sensitivity and Specificity of alternative diagnostic tools against nasoendoscopy

Diagnostic Test	Sensitivity	Specificity	N
Clinical Exam			
NOI[46]	22%	88%	154
Rhinomanometry			
without decongestant[50]	81%	34%	71
with decongestant[50]	83%	83%	52
Lateral Cephalogram			
adenoid size[45]	86%	41%	48
A/N ratio[45]	41%	95%	48
adenoid – turbinate airway[45]	61%	68%	48
airway-palate ratio[45]	66%	96%	48
airway size (McNamara line)[47]	75%	86%	30
subjective assess[27]	70%	55%	40
subjective assess[48]	70%	52%	70
Video Fluoroscopy			
Nasopharynx during function [27]	100%	90%	40
Nasopharynx during function [48]	100%	93%	70
Multi-row detector CT			
Multi-plane render [49]	92%	97%	29

2.7 Figures

Figure 2-1: literature search and selection flow diagram

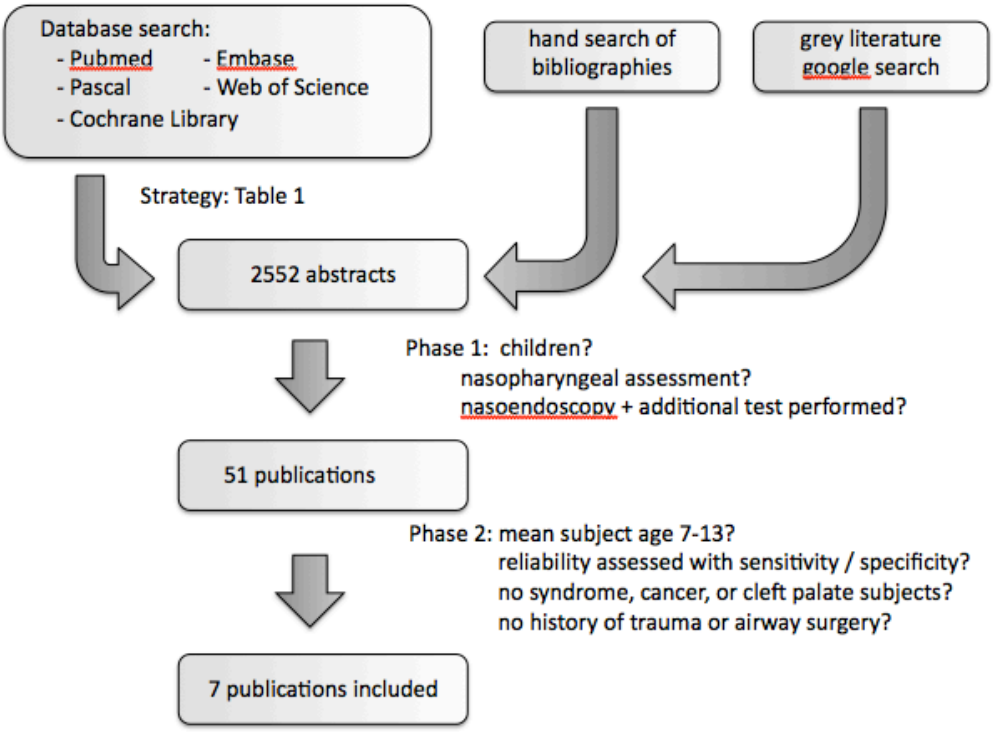
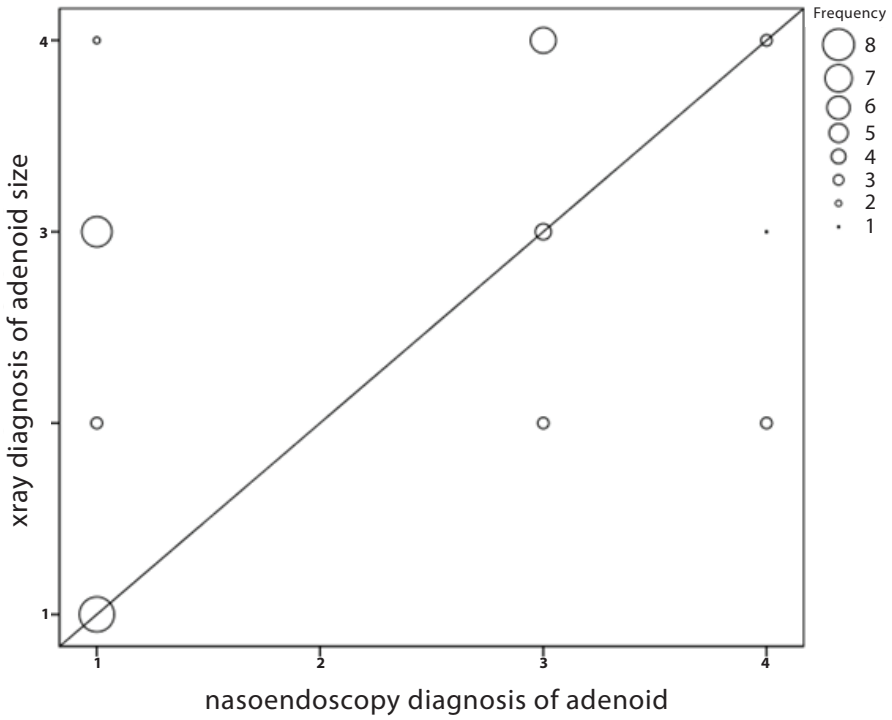


Figure 2-2: distribution of adenoid size evaluated by lateral cephalogram vs nasoendoscopy



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Chapter 3: Accuracy and Reliability of CBCT Imaging for Assessing Adenoid Hypertrophy

3.1 Introduction

Adenoid hypertrophy is one of the most common etiologies of nasopharyngeal obstruction. Nasopharyngeal obstruction has been associated with mouth breathing[1] and sleep disordered breathing (SDB).[1-3] Both mouth breathing and SDB are significant conditions the orthodontist should be prepared to identify.

Mouth breathing has been proposed as a significant factor for altered craniofacial growth.[4] The description of this pattern includes narrow maxillary arch, posterior crossbite, long face height with clockwise mandibular growth rotation, anterior open bite and mandibular retrognathia.[5-7] Each of these anatomical presentations are considered esthetic and/or functional indications for orthodontic treatment, and may be prevented by early intervention.[8]

SDB may cause systemic problems such as reduced systemic growth[9], systemic hypertension[10] and pulmonary hypertension[11] that may cause right or left ventricular hypertrophy respectively[12,13], hyperactivity and attention deficit[14], aggression[14], and reduced grades in school[15].

Diagnosis of upper airway dysfunction starts with clinical history – chronic snoring, breathing interruption during sleep, growth rate, tendency to fall asleep during the day, behavioral difficulties and chronic runny nose.[16] The current reference standard for assessing the nasal cavity and nasopharynx is nasoendoscopy (NE)[17] with utilization of a standardized grading system for evaluation.[18,19] However, NE must be conducted by a otorlarongologist and is outside the scope of orthodontic practice.

Traditionally, orthodontists have used lateral cephalograms to supplement their clinical evaluation of hypertrophic adenoids. However, a previous systematic review could not identify a reliable 2D assessment of the adenoids from a lateral cephalogram[20] and

recommended that orthodontists should seek an alternative low risk, simple and valid diagnostic tool to screen for potential upper airway constriction.

Cone-beam computerized tomography (CBCT) provides a low cost, easily accessible and relatively low radiation 3D evaluation of craniofacial structures,[21,22] and is routinely used for diagnosis and treatment planning more complicated orthodontic cases.[23-25] Dimensions of the nasopharyngeal airway (air cavity distance surrounded by soft tissue) are accurate for CBCT imaging.[26] Volumetric measurement errors have been reported to range from 0% to 5% compared with known physical airway phantoms.[27] As of yet, the accuracy and reliability of CBCT imaging in determining the magnitude of a nasopharyngeal obstruction from hypertrophic adenoids has not been evaluated.

The objective of the present study is to evaluate the accuracy and reliability of CBCT imaging for evaluating adenoid obstruction by comparing CBCT diagnosis against NE diagnosis.

3.2 Methods

CBCT diagnostic efficacy for adenoid hypertrophy was evaluated with a prospective/retrospective, cross-sectional agreement study. Protocol approval was granted by the University of Alberta Health Research Ethics board (Pro00020649). Subjects were recruited from a tertiary referral center, the University of Alberta multi-disciplinary upper airway dysfunction clinic. Inclusion / exclusion criteria were:

- male and female patients age 6-15 – age range was chosen because 1) it represents the range typically seen in orthodontic practice, and 2) during this age range orthodontic interventions may impact airway function (ex rapid maxillary expansion)
- orthodontic patients with upper airway concerns or ENT patients with suspected orthodontic and/or craniofacial development concerns
- exclude subjects with confirmed syndromes or neurological disorders
- exclude subjects with any previous treatment for airway obstruction

- exclude children experiencing concomitant acute upper respiratory tract infections, and postpone the procedure was for at least two weeks to capture a true baseline examination state

Study recruitment began in September 2011 and continued until October 2012. Sample size was not determined a priori but the goal was to include as many participants as possible in the defined period. All consecutively evaluated patients meeting the criteria were included in the study. By recruiting subjects evenly throughout an entire calendar year the effects of confounders such as seasonal allergies were likely accounted for.

At examination, an orthodontist and otolaryngologist assessed all patients on the same day each using CBCT imaging and NE respectively. Due to the complex craniofacial problems common to these subjects (transverse, vertical, and antero-posterior concerns), CBCT imaging was taken instead of panorex, lateral ceph, and PA ceph. Evaluations were postponed for any subjects experiencing acute nasal symptoms, such as a cold or active allergy flair-up, to ensure accurate baseline assessments.

Nasoendoscopic evaluation

NE was also performed in the upright position using a 2.2mm flexible tube endoscope (vs. rigid endoscopy) allowing the otolaryngologist to view all the way to the epiglottis. Topical decongestion (0.05% Xylometazoline) and anesthesia (4% lignicaine) were applied using a cotton-tipped applicator. The examinations were prospectively recorded on a digital image-capturing unit, and electronically archived. The otolaryngologist documented the size of the adenoids and other findings using an individual patient information sheet. This formed the basis of dictation of the clinic date in a standard format.

Despite the prospective assessment, nasoendoscopy findings were compiled by retrospective extraction from the clinical reports. Severity of adenoid obstruction was evaluated on the video endoscopy images using a previously validated subjective 4 point scale.[17,18] In this scale grade 1 = <25% obstruction, grade 2 = 25-50%, grade 3 = 50-

75%, and grade 4 = >75%. (Figure 3-1) When reports were not clear regarding adenoid size classification, the archived nasoendoscopy video documentation were re-evaluated to clarify the diagnosis.

CBCT evaluation

CBCT images were taken in the upright position with a 12-inch field of view, 300μm voxel, and 8.9sec scan time. CBCT images were acquired within two to three hours after NE; decongestant delivered by the otolaryngologist was still effective during CBCT evaluation thus ensuring consistency of the nasal tissues during evaluation.

All CBCT images were coded for blinding and randomized for prospective evaluation by an independent consultant who kept the code hidden until all evaluations were complete. Severity of adenoid obstruction was evaluated on CBCT images using the same scoring system as for the NE evaluation.[17,18] In this scale grade 1 = <25% obstruction, grade 2 = 25-50%, grade 3 = 50-75%, and grade 4 = >75%. (Figure 3-1) Specifically on CBCT, adenoid size was evaluated using slices in all three planes of space (as opposed to 3D volume rendering); the mid-saggital slice was used as the starting point of assessment and most diagnostically useful, but the diagnosis was collated with slices from the axial and coronal places as well. All DICOM visualizations were made using OsiriX 64-bit imaging software (Geneva, Switzerland).

CBCT assessments were completed by a team of 4 evaluators: an oral & maxillofacial radiologist (OMFR), an airway orthodontist (AO) who participates in the multi-disciplinary team, an academic orthodontist who's primary research is in 3D imaging (3DO), and a highly experienced private practice orthodontist (PPO) comfortable with CBCT imaging. Each evaluator was specifically chosen to represent a unique set of clinical and radiographic experience. All evaluators were blinded to the subject's identity and clinical history, evaluated the images in a unique random order, and evaluated each image 3 separate times separated by a minimum of 7 day wash-out period. All evaluators reviewed the CBCT images using the same computer hardware and software.

Statistical analysis

Accuracy of CBCT images for diagnosing adenoid obstruction was statistically analyzed in two ways. First, agreement between CBCT and NE was evaluated using intra-class correlation coefficient (ICC) statistics based the 4 point grading system. 95% confidence intervals were calculated for all ICC's. Second, the 4-point scale was converted to a binary diagnosis of "yes" / "no" for adenoid hypertrophy. Two-by-two contingency tables for individual observers were generated and used to compute sensitivity / specificity. Patients classified as moderate or severe (Grades 3 or 4) were considered positively diagnosed with adenoid obstruction.[17]

Reliability of CBCT imaging was determined by quantifying the level of agreement between the 4 evaluator's assessments. ICC statistics were calculated to quantify intra-observer (IAO) and inter-observer agreement (IEO). ICC statistics were computed using SPSS Statistics software package (version 20.0, Chicago, USA)

3.3 Results

In total, 39 consecutively evaluated subjects between the ages of 6.3 to 15.8 years (mean = 11.5 ± 2.8) were assessed (Figure 3-1). With NE, 17 subjects were diagnosed with grade 1 adenoids, 10 subjects with grade 2, 7 subjects with grade 3, and 5 subjects with grade 4. This distribution equated to 12 subjects with clinically significant adenoid hypertrophy, while 27 were considered healthy. Intra-observer and inter-observer reliability was not evaluated for NE.

Reliability of repeated CBCT evaluations (intra-observer agreement) on the 4-point scale demonstrated very good agreement. (Table 3-1) The maxillofacial radiologist (OMFR), academic 3D orthodontist (3DO), and airway orthodontist (AO) had very good intra-observer agreement (IAO) – that is, were all very consistent between repeated evaluations (ICC = 0.813-0.819; 95% CI ± 0.137-0.142). The private practice orthodontist (PPO) had good IAO (ICC = 0.740, 95% CI ± 0.134). Despite the PPO seeming poorer

than the other evaluators, there was no statistical difference as the 95% confidence intervals for all evaluators overlapped (Figure 3-2), although the lower boundary 95% CI was only 0.606. In addition to strong intra-observer reliability, CBCT reliability was further collaborated by strong inter-observer agreement (EO) – that is, agreement between evaluators (ICC = 0.836 ± 0.084).

Accuracy of CBCT evaluations (agreement between CBCT with NE evaluations) was also strong across evaluators (ICC = 0.743-0.819, Table 3-2). (Table 3-2) While the PPO again had the lowest level of CBCT agreement with NE (ICC = 0.743; 95% CI ± 0.183), the 95% confidence intervals of all evaluators comfortably overlapped (Figure 3-3).

When evaluations were transformed into clinically relevant binary diagnoses of diseased vs. healthy (Table 3-3), the sensitivity / specificity of CBCT imaging for evaluating adenoid hypertrophy was excellent. (Table 3-4) All evaluators achieved sensitivity values of 83% or more, and specificity values of 88% or better were demonstrated. As a group of evaluators (Figure 3-4), CBCT demonstrated 88% sensitivity and 93% specificity for identifying clinically relevant adenoid hypertrophy.

Positive predictive values (PPV) and negative predictive values (NPV) were not calculated because they were deemed inappropriate statistics for this sample. PPV and NPV are population dependent statistics that are directly related to disease prevalence.[28] No reliable prevalence data regarding adenoid hypertrophy could be found, as population estimates range widely from 19%[29] to 58%.[30] Therefore any PPV and NPV calculated from this sample could be misleading and false.

3.4 Discussion

2D radiographs are at best fair for evaluating the nasopharyngeal airway (see thesis section V systematic review). A previous systematic review [20] suggested that an alternative radiographic technique, one that can be used for routine for orthodontic diagnosis and treatment planning, is needed for evaluating adenoid size. The objective of

this study was to evaluate the accuracy and reliability of CBCT for screening adenoid hypertrophy.

Since ICC was the primary statistical analysis, a quick review of ICC interpretation may be helpful. The generally accepted guideline for ICC interpretation[31] suggests ICC >0.75 = excellent agreement, ICC between 0.4 - 0.74 = good to fair agreement, and ICC <0.4 = poor agreement.

This study demonstrated that CBCT imaging was reliable (Figure 3-2) for evaluating adenoid size both within evaluators (IAO ICC = 0.85, 95% CI ± 0.08) and between evaluators (IEO ICC = 0.84 ± 0.08). Impressively the variation within observers and between observers was almost identical.

In addition, this study demonstrated that CBCT was accurate (Figure 3-3) for evaluating adenoid size compared to the reference-standard NE (CBCT vs. NE ICC = 0.80, 95% CI ± 0.15). As a screening tool CBCT demonstrated very good sensitivity (88%) – the ability to detect true disease from a population. Furthermore CBCT displayed excellent specificity (93%) – the ability to detect true disease from a population. These findings suggest CBCT is a valid tool for screening subjects with clinically relevant nasopharyngeal obstruction.

This study design permitted preliminary probing into the role that clinical and radiographic experience plays in screening for adenoid hypertrophy with CBCT imaging. Keeping in mind that only one individual per category was assessed the findings need to be considered carefully. The OMFR, AO, 3DO, had strong reliability (IAO) evaluating CBCT images and good accuracy against NE findings. (Table 3-2). The reliability lower limit 95% CI was well above the recommended 0.75 cut-off value[31], while the accuracy 95% CI was slightly below, but still at the upper range of “fair to good”. For all effective purpose, these three evaluators with advanced training were completely equivalent in their ability to grade adenoid size on 4-point scale, and were all considered acceptably accurate and reliable.

When viewed on the 4-point size evaluation scale, interpreting the results of the PPO was more challenging. Visually, the PPO's evaluations did not seem as reliable (Figure 3-2), although accuracy was similar (Figure 3-3). On one had there was no statistical difference between the reliability of the 4 evaluators, since there was overlap between the 95% confidence intervals. But on the other hand, the lower limit of the 95% confidence interval for the PPO fell substantially below the recommended cut-off of 0.75[31]. Therefore, despite the lack of statistical difference, the private practice orthodontist should not be considered as reliable for evaluating adenoid size on a 4-point scale, although the accuracy seems within range.

However, when viewed in the context as a clinically relevant diagnosis (binary diseased vs. healthy), the individual representing PPO in this study achieved equal sensitivity and specificity as the other three evaluators (Table 3-4). What must be kept in mind is that the PPO evaluated in this study has invested considerable time taking continuing education in CBCT imaging and airway related disorders. The findings of the "private practice orthodontist" in this study may not be representative of the average clinician, but instead represent a high water mark. Therefore an astute PPO – one who is willing to invest considerable time into 3D radiographic continuing education – can realistically aspire to accurately and reliably secondarily screen for clinically relevant adenoid hypertrophy when the imaging has been acquired for other orthodontic purposes.

Orthodontists have an obvious interest in upper airway management as a key component to achieving their treatment outcomes given the relationship between craniofacial growth, development of malocclusion, and nasopharyngeal obstruction. Since a well-trained PPO can identify clinically relevant adenoid hypertrophy with reasonable accuracy, orthodontists may have an important role as early detectors of mild to moderate pediatric SDB (SDB). While several instances of pediatric SDB are often identified early in life, mild to moderate cases may go undiagnosed by primary care physicians or pediatricians. In this capacity orthodontists may significantly help improve

their patient's systemic health, quality of life, and cognitive-behavioral development by a timely appropriate referral.

As potential early detectors of nasopharyngeal obstruction and pediatric SDB, orthodontists should become familiar with identifying common symptoms and risk factors. Common symptoms include: altered craniofacial growth[6,7], snoring[32], mouth breathing[1], suborbital venous pooling, headaches, rhinorrhea, and attention deficit[14,15]. Common risk factors for developing POSA include: asthma[1,33], obesity[2,3,34], chronic allergies[4,35], parent or housemate that smoke[5-7,36], and pre-term birth[8,37]. If an orthodontist combines a thorough clinical history with reliable CBCT imaging, they should have excellent success screening patients who require further otolaryngology and sleep medicine work-ups.

Despite the high degree of accuracy and reliability of CBCT for evaluating adenoid size, orthodontists should be mindful of its limitations. First, the findings of this study cannot be universally applied to all anatomical structures of the airway. Compared to other soft tissue craniofacial structures adenoids are more stable in size and a "snap shot" CBCT image is accurately representative. In contrast, the oropharynx space is extremely dynamic because of the tongue's mobility, and imaging taken mere seconds apart can be highly variable.[9,38] Similarly the nasal passage is high dynamic due to physiologic nasal cycles of the turbinate, and may also appear very different if images are retaken after 30 minutes.[10,39] Because of these limitations and anatomical differences it is absolutely critical for orthodontists to understand that CBCT imaging alone is completely unable to diagnose SDB, even though CBCT is accurate and reliable for diagnosing adenoid hypertrophy.

In addition to anatomical limitations, it is uncertain whether the accuracy and reliability of CBCT would extend to children younger than 6 years old. Typically children with moderate to severe sleep disordered breathing are diagnosed at a very early age, often within the first year of life. However, this is unlikely to be an issue – because of the radiation delivery CBCT will never be a replacement for NE. The indication for acquiring a CBCT image is for orthodontic diagnosis, which can then be secondarily evaluated for

adenoid hypertrophy. Since children are unlikely to receive orthodontic evaluated before the age of 6, the findings of this study are valid for the population likely to be receiving a CBCT image.

While at first glance the sample size of this study may appear small and therefore underpowered. However, the ICC confidence intervals are tight, especially among the three highly trained evaluators (OMFR, AO, 3DO). It is highly unlikely that increasing the sample size will improve the confidence intervals. Therefore, despite the smaller sample size, the study's findings are more than likely valid and useful for clinical application. Regarding the PPO category due to the large confidence interval the values could be modified significantly with an increased sample size. This should be addressed in future studies.

However, other weaknesses in methodology remain. First, reliability was not described for NE evaluation. Second, the method of collecting nasoendoscopy data had to be compiled retrospectively, even though the otolaryngologist documented the findings prospectively. Third, the private practice orthodontist may not have been representative of an "average" orthodontist due to his extensive continuing education training and personal interest in airway. Future investigations ideally should tighten the prospective methodology in addition to performing repeated and blinded NE assessments of adenoids ideally with multiple evaluators. This protocol would strengthen the methods and allow intra-observer and inter-observer reliability of nasoendoscopy to be described, and then contrasted against CBCT reliability.

3.5 Conclusions

- CBCT images are accurate for evaluating adenoid size compared to nasoendoscopy (ICC = 0.80, 95% CI ± 0.15)
- CBCT evaluations are reliable between repeated evaluations from a single individual (intra-observer ICC 0.85, 95% CI ± 0.08), and evaluated between multiple individuals (inter-observer ICC = 0.836 ± 0.084)
- CBCT can accurately identify clinically relevant adenoid hypertrophy with 88% sensitivity and 93% specificity
- In the hands of orthodontists trained to look at adenoid size in relation to the post nasal space the CBCT approaches the accuracy and reliability of NE

3.6 Tables

Table 3-1: Reliability of CBCT for diagnosing adenoid size

	Agreement between repeated CBCT evaluations (ICC ± 95% CI)
Maxillofacial Radiologist	0.886 ± 0.070
Airway Orthodontist	0.892 ± 0.067
Academic 3D Orthodontist	0.896 ± 0.065
Private Practice Orthodontist	0.740 ± 0.134
Average Intra-observer Agreement	**0.85 ± 0.08**
Overall Inter-observer Agreement	**0.836 ± 0.084**

Table 3-2: Accuracy of CBCT imaging for diagnosing adenoid size

	Agreement between CBCT and NE evaluations (ICC ± 95% CI)
Maxillofacial Radiologist	0.813 ± 0.140
Airway Orthodontist	0.814 ± 0.142
Academic 3D Orthodontist	0.819 ± 0.137
Private Practice Orthodontist	0.743 ± 0.183
Average	**0.80 ± 0.15**

Table 3-3: 2x2 tables comparing CBCT vs. NE diagnosis of adenoid hypertrophy

a. Radiologist

	NE (+)	NE (-)
CBCT (+)	10	2
CBCT (-)	2	25

b. Airway Orthodontist

	NE (+)	NE (-)
CBCT (+)	10	1
CBCT (-)	2	26

c. Academic 3D Orthodontist

	NE (+)	NE (-)
CBCT (+)	11	2
CBCT (-)	1	25

d. Private Practice Orthodontist

	NE (+)	NE (-)
CBCT (+)	11	2
CBCT (-)	1	24

Table 3-4: Sensitivity / specificity of CBCT for diagnosing adenoid size evaluated against nasoendoscopy

	Sensitivity	Specificity
Maxillofacial Radiologist	83.3%	92.6%
Airway Orthodontist	83.3%	96.2%
Academic 3D Orthodontist	91.7%	92.6%
Private practice Orthodontist	91.7%	88.9%
Average	**88%**	**93%**

Table 3-5: 4x4 contingency table of CBCT vs NE adenoid size for all evaluators

	NE1	NE2	NE3	NE4
CBCT1	55	17	3	0
CBCT2	11	17	4	0
CBCT3	1	2	11	5
CBCT4	1	4	11	15

3.7 Figures

Figure 3-1: adenoid size in CBCT mid-sagittal slice

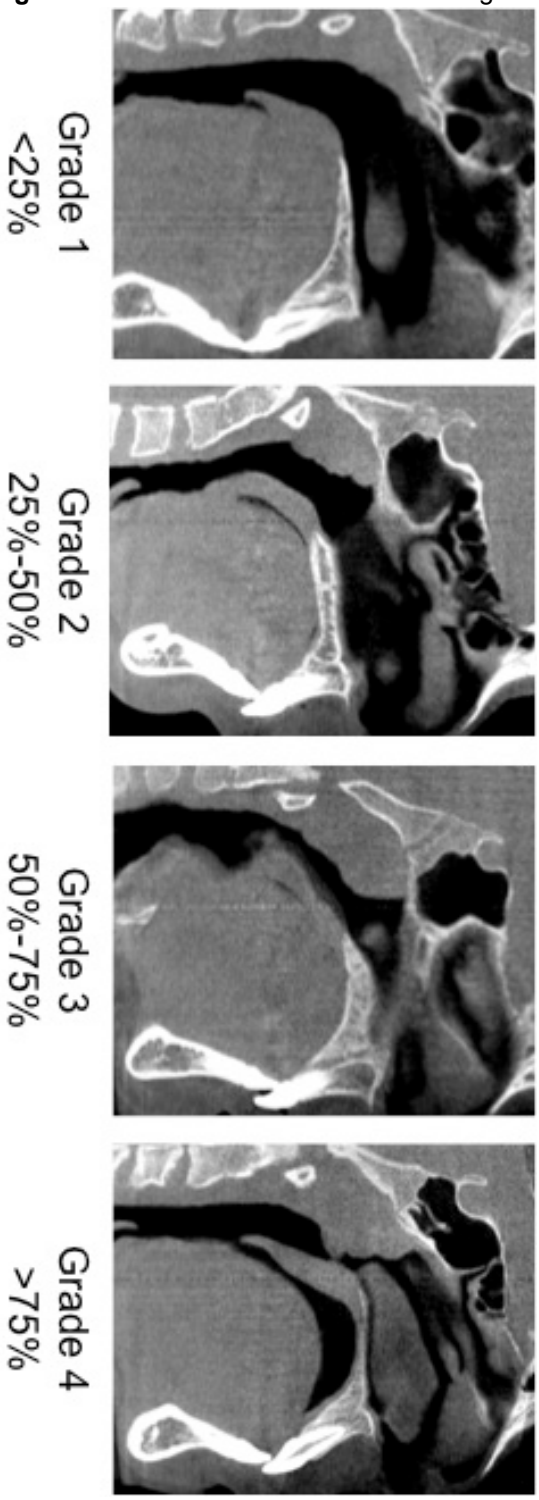


Figure 3-2: CBCT Reliability – Agreement Between Repeated CBCT evaluations

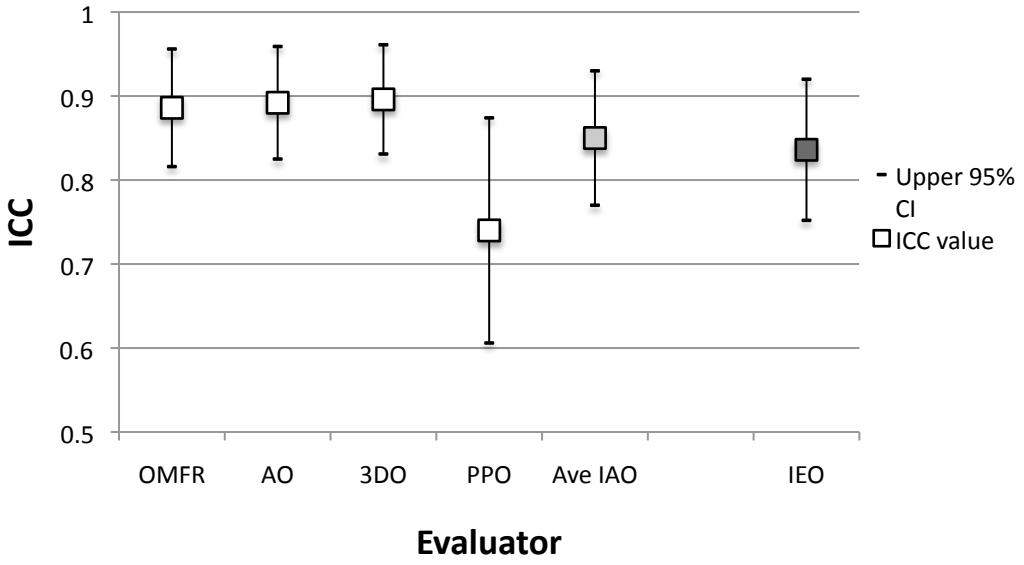


Figure 3-3: CBCT Accuracy – Agreement Between CBCT and NE evaluations

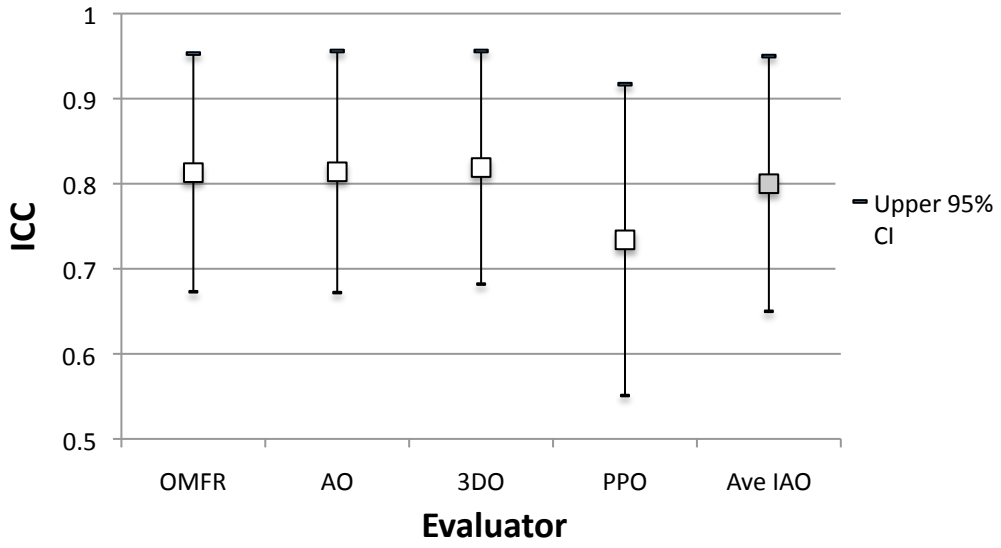
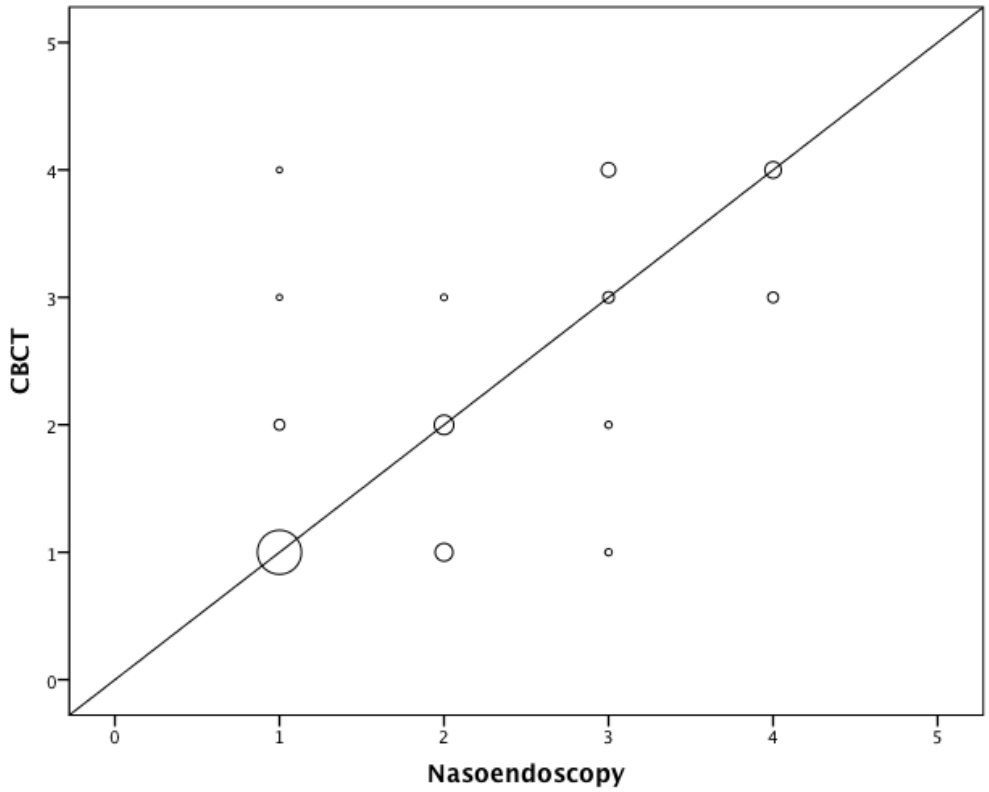


Figure 3-4: distribution of adenoid size evaluated by CBCT vs nasoendoscopy for all evaluators



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Chapter 4: Conclusions

4.1 Evaluation of the Null Hypothesis

The primary objective of this investigation was to evaluate the reliability and accuracy of CBCT imaging for evaluating adenoid size. Specifically, CBCT images were compared against nasoendoscopy diagnosis. The primary null hypothesis was:

H_o: CBCT imaging is unable to accurately and reliably evaluate adenoid hypertrophy

H_A: CBCT imaging is an accurate and reliable tool to screen for adenoid hypertrophy

The secondary objective was to assess whether clinical experience impacts the accuracy and reliability of evaluating CBCT images. The secondary null hypothesis was:

H_O: Clinical experience does not influence accuracy and reliability of CBCT interpretation

H_A: Clinical experience does influence accuracy and reliability of CBCT interpretation

The following key findings were observed:

1. CBCT images are accurate for evaluating adenoid size compared to nasoendoscopy (ICC = 0.80, 95% CI ± 0.15)

2. CBCT evaluations are reliable between repeated evaluations from a single individual (intra-observer ICC 0.85, 95% CI ± 0.08), and evaluated between multiple individuals (inter-observer ICC = 0.836 ± 0.084)
3. CBCT can accurately identify clinically relevant adenoid hypertrophy with 88% sensitivity and 93% specificity
4. In the hands of orthodontists trained to look at adenoid size in relation to the post nasal space the CBCT approaches the accuracy and reliability of NE

On the basis of these observations the primary null hypothesis was rejected, and the alternative hypothesis was accepted. CBCT imaging is a reliable and valid tool for identifying adenoid hypertrophy.

Furthermore, the secondary null hypothesis was rejected, and the secondary alternative hypothesis was accepted. Accuracy and reliability of CBCT evaluations are influenced by experience, but with adequate training does not seem to affect clinical performance

4.2 Clinical Significance and Implications

Prior to the development of CBCT, orthodontists lacked an accurate and reliable tool for screening adenoid size.[1] The findings of this study validate CBCT imaging as an accurate and reliable screening tool for evaluating adenoid size. Furthermore, this study demonstrated that orthodontists of various backgrounds – including dedicated private practice clinicians – can become adequately trained to very accurately screen clinically relevant adenoid hypertrophy.

Relative to other imaging modalities, CBCT is superior to clinical examination alone and lateral cephalometry (Table 4-1) for evaluating adenoid size. Furthermore, CBCT is able to achieve comparable sensitivity and specificity to video fluoroscopy and multi-row detector CT imaging (Table 4-1), but does so at a fraction of the radiation depending on the imaging parameters. CBCT imaging provides a unique balance of accessibility, reliability, and accuracy at a relative low radiation dose. This is not to say CBCT imaging ought to be applied universally, simply to screen for adenoid hypertrophy in every patient. Rather when clinical exam and medical history are highly suggestive for nasopharyngeal obstruction, or when when 3D imaging is indicated for specific orthodontic diagnosis and treatment planning (i.e. impacted teeth, TMJ evaluation, orthognathic surgery)[2], orthodontists can confidently perform secondarily evaluations of adenoid size.

Furthermore, CBCT imaging will never (and should never) be considered a replacement to nasoendoscopy. However, given the limited access to otolaryngologists, the accuracy and reliability of CBCT imaging further solidifies the orthodontist's important role as an early detector and screener of pediatric airway problems. As a capable an early detector orthodontists are uniquely positioned to provide high quality referrals in need of ENT evaluation and concurrently reduce the number of false positive referrals.

4.3 Recommendations for Future Research

1. CBCT imaging is highly reliable for evaluating adenoid size and may provide a diagnosis that can improve orthodontic outcomes and overall health. However, CBCT imaging is not entirely benign. The use of ionizing radiation always caries a certain amount of risk and therefore should used judiciously, always conforming principles of ALARA. Therefore the development systematic and validated clinical algorithms are to help orthodontists identify

which patients are most likely to benefit from CBCT imaging are recommended.

2. Adenoid hypertrophy is only one possible cause of airway obstruction. Septum deviation, turbinate hypertrophy, cocha bullosa, lingual tonsil hypertrophy, and oropharyngeal constriction could all contribute to airway problems, and can be visualized on CBCT images. Future research investigating the use of CBCT for assessing other nasal and oropharyngeal problems is recommended.

4.4 Tables

Table 4-1: Sensitivity and Specificity of CBCT compared to other tests for diagnosing adenoid hypertrophy

Diagnostic Test	Sensitivity	Specificity	N
Clinical Exam			
NOI[46]	22%	88%	154
Rhinomanometry			
without decongestant[50]	81%	34%	71
with decongestant[50]	83%	83%	52
Lateral Cephalogram			
adenoid size[45]	86%	41%	48
A/N ratio[45]	41%	95%	48
adenoid – turbinate airway[45]	61%	68%	48
airway-palate ratio[45]	66%	96%	48
airway size (McNamara line)[47]	75%	86%	30
subjective assess[27]	70%	55%	40
subjective assess[48]	70%	52%	70
Video Fluoroscopy			
Nasopharynx during function [27]	100%	90%	40
Nasopharynx during function [48]	100%	93%	70
Multi-row detector CT			
Multi-plane render [49]	92%	97%	29
CBCT			
percent obstruction	88%	93%	39

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Appendix A: Systematic Review Protocol, Database Search Terms and Strategies

Question:

1) what diagnostic tests are available for assessing the upper airway?
2) What is the sensitivity and specificity of these studies compared to nasoendoscopy?

Purpose in Thesis: provide numerical data to compare against the sensitivity / specificity results that will be generated in my clinical study

P: children age 3-18 with suspected upper airway dysfunction

I: any quantified, reproducible diagnostic tests of the adenoids or nasal septum

C: diagnosis with nasoendoscopy

O: sensitivity / specificity analysis

Search Strategy

Pubmed

1) ((upper OR nasal OR nasopharyngeal) AND airway) OR adenoid* OR adenoid [MeSH] OR nasal septum OR nasal septum [MeSH] OR nasopharynx OR nasopharynx [MeSH] OR nasal obstruction [MeSH]

2) diagnostic OR diagnosis OR diagnosis [MeSH] OR assess* OR test OR evaluat* OR exam* OR investigat* OR rhinometry OR radiograph OR x-ray OR cephalomet* OR cephalometry [MeSH] OR fluoroscop* OR fluoroscopy [MeSH] OR tomography OR tomography, X-ray [MeSH] OR CT OR CBCT OR magnetic resonance OR MRI OR magnetic resonance imaging [MeSH]

3) endoscop* OR fiberoptic OR endoscopy [MeSH]

4) nasoendoscop*

5) 1 AND 2

6) 1 AND 3

7) 4 OR 6

8) 5 AND 7

Limits: human, children and adolescents (age 6-18), NOT cancer

Inclusion Criteria	Exclusion Criteria
• Subjects age 6-15	• Adults
• Sensitivity / specificity comparison to nasoendoscopy	• Syndromes or atypical development (ie. clefts, flaccid musculature)
	• Cancer or syndromes
	• History of airway surgery or trauma

EMBASE

1) ((upper OR nasal OR nasopharyngeal) AND airway) OR adenoid$ OR adenoid [MeSH] OR nasal septum OR nasal septum [MeSH] OR nasopharynx OR nasopharynx [MeSH] OR nose obstruction [MeSH]

2) diagnostic OR diagnosis OR diagnosis [MeSH] OR assess$ OR test OR evaluat$ OR exam$ OR investigat$ OR rhinometry OR radiograph OR x-ray OR cephalomet$ OR cephalometry [MeSH] OR fluoroscop$ OR fluoroscopy [MeSH] OR tomography OR tomography [MeSH] OR CT OR CBCT OR magnetic resonance OR MRI OR nuclear magnetic resonance imaging [MeSH]

3) endoscop$ OR fiberoptic OR endoscopy [MeSH]

4) nasoendoscop$

5) 1 AND 2

6) 1 AND 3

7) 4 OR 6

8) 5 AND 7

Limits:

Cochrane Library

1) ((upper OR nasal OR nasopharyngeal) AND airway) OR adenoid* OR adenoid [MeSH] OR nasal septum OR nasal septum [MeSH] OR nasopharynx OR nasopharynx [MeSH] OR nasal obstruction [MeSH]

2) diagnostic OR diagnosis OR diagnosis [MeSH] OR assess* OR test OR evaluat* OR exam* OR investigat* OR rhinometry OR radiograph OR x-ray OR cephalomet* OR cephalometry [MeSH] OR fluoroscop* OR fluoroscopy [MeSH] OR tomography OR tomography, X-ray [MeSH] OR CT OR CBCT OR magnetic resonance OR MRI OR magnetic resonance imaging [MeSH]

3) endoscop* OR fiberoptic OR endoscopy [MeSH]

4) nasoendoscop*

5) 1 AND 2

6) 1 AND 3

7) 4 OR 6

8) 5 AND 7

Web of Science

1) ((upper OR nasal OR nasopharyngeal) AND airway) OR adenoid* OR nasal septum OR nasopharynx OR nasal obstruction

2) diagnostic OR rhinometry OR radiograph OR x-ray OR cephalomet* OR fluoroscop* OR tomography OR CT OR CBCT OR magnetic resonance OR MRI

3) endoscop* OR fiberoptic

4) nasoendoscop*

5) 1 AND 2

6) 1 AND 3

7) 4 OR 6

8) 5 AND 7

9) cancer OR valopharangeal OR valopharynx OR trauma OR “cleft lip” OR “cleft palate”

10) 8 NOT 9

Limit to Subject Area: otorhinolaryngology, pediatrics, medicine, respiratory system, allergy, immuneology, radiology nuclear medicine medical imaging, dentistry

Date: Tuesday, October 04, 2011 10:05:24 PM Print Close

ID:Pro00020649
Status:Approved

1.1 Study Identification

*All questions preceded by a red asterisk * are required fields. However, answering only the required fields may not provide sufficient information for the REB in order to evaluate your application.*
Please answer all presented questions that will reasonably help to describe your study or proposed research.

1.0 * **Short Study Title** *(restricted to 250 characters)*:
CBCT Imaging for Diagnosis of Upper Airway Dysfunction

2.0 * **Complete Study Title** *(can be exactly the same as short title)*:
Evaluation of Cone-beam Computerized Tomography (CBCT) for Diagnosis of Adenoid Hypertrophy an Deviated Nasal Septum

3.0 * **Select the appropriate Research Ethics Board (***Detailed descriptions are available by clicking the HELP link in the upper right hand corner of your screen***):**
HREB Biomedical

4.0 * **Is the proposed research:**
Funded (Grant, subgrant, contract, internal funds, donation or some other source of funding)

5.0 * **Name of Principal Investigator** *(at the University of Alberta, Covenant Health, or Alberta Health Services)*:
Carlos Flores Mir

6.0 **Investigator's Supervisor** *(required for applications from undergraduate students, graduate students, post-doctoral fellows and medical residents to Boards 1, 2, 3. HREB does not accept applications from student PIs)*

7.0 * **Type of research/study:**
Graduate Student - Thesis, Dissertation, Capping Project

8.0 **Study Coordinators or Research Assistants:** People listed here can edit this application and will receive all HERO notifications for the study:

Name	Employer
Joanne Lafrance	MH Dentistry

9.0 **Co-Investigators:** People listed here can edit this application but do not receive HERO notifications unless they are added to the study email list:

Name	Employer
Paul Major	MH Dentistry
Hamdy El-Hakim	MH Surgery
Manisha Witmans	MH Pediatrics
Michael Major	Student

10.0 **Study Team** *(Co-investigators, supervising team, other study team members):* People listed here cannot edit this application and do not receive HERO notifications:

Last	First Name	Organization	Role	Phone	Email

Name				
Alsufyani Noura	University of Alberta	Collaborative Researcher		nourasuf@gmail.com
Korayem Mohammed	University of Alberta	Collaborative Researcher	(780) 492-4469	mkorayem@hotmail.com
MacLean Joanna	University of Alberta	Collaborative Researcher		joanna.maclean@albertahealthservices.ca

1.2 Additional Approval

1.0 * **Departmental Review:**
MH Dentistry

2.0 **Internal Review:**

1.3 Study Funding Information

1.0 * **Type of Funding:**
Internal Funds (eg. Start-up funds, TLEF, Operational, etc)

If OTHER, provide details:

2.0 * **Indicate which office administers your award.** *(It is the PI's responsibility to provide ethics approval notification to any office other than the ones listed below)*
Other

If OTHER, provide details:

3.0 * **Funding Source**

3.1 Select all sources of funding from the list below:
There are no items to display

3.2 If not available in the list above, write the Sponsor/Agency name(s) in full (you may add multiple funding sources):
View McIntyre Funds

4.0 * **Indicate if this research sponsored or monitored by any of the following:**
Not applicable

If applicable, indicate whether or not the FDA Investigational New Drug number or FDA Investigational Device Exception is

required:

The researcher is responsible for ensuring that the study complies with the applicable US regulations. The REB must also meet particular review criteria and this application will likely receive full board review, regardless of level risk.

1.5 Conflict of Interest

1.0 * **Are any of the investigators or their immediate family receiving any personal remuneration (including investigator payments and recruitment incentives but excluding trainee remuneration or graduate student stipends) from the funding of this study that is not accounted for in the study budget?**

○ Yes ◉ **No**

If YES, explain:

2.0 * **Do any of investigators or their immediate family have any proprietary interests in the product under study or the outcome of the research including patents, trademarks, copyrights, and licensing agreements?**

○ Yes ◉ **No**

3.0 **Is there any compensation for this study that is affected by the study outcome?**

○ Yes ◉ **No**

4.0 **Do any of the investigators or their immediate family have equity interest in the sponsoring company? (This does not include Mutual Funds)**

○ Yes ◉ **No**

5.0 **Do any of the investigators or their immediate family receive payments of other sorts, from this sponsor (i.e. grants, compensation in the form of equipment or supplies, retainers for ongoing consultation and honoraria)?**

○ Yes ◉ **No**

6.0 **Are any of the investigators or their immediate family, members of the sponsor's Board of Directors, Scientific Advisory Panel or comparable body?**

○ Yes ◉ **No**

7.0 **Do you have any other relationship, financial or non-financial, that, if not disclosed, could be construed as a conflict of interest?**

○ Yes ◉ **No**

If YES, explain:

Important
If you answered YES to any of the questions above, you may be contacted by the REB for more information or asked to submit a Conflict of Interest Declaration.

1.6 Research Locations and Other Approval

1.0 * **List the locations of the proposed research, including recruitment activities. Provide name of institution or organization, town, or province as applicable** (e.g. On campus, Alberta public elementary schools, shopping malls, doctors' offices in Lesser Slave Lake and Lac La Biche, AHS facilities in Zone 5, post-secondary students at UBC, UA, UT, McGill and Dalhousie, internet websites, etc.)**:**
University of Alberta Graduate Orthodontic Clinic

2.0 * **Indicate if the study will utilize or access facilities, programmes, resources, staff, students, specimens, patients or their records, at any of the sites affiliated with the following** *(select all that apply):*
Alberta Health Services Institutions and Facilities in the GREATER EDMONTON

List all facilities or institutions as applicable:
Study subjects will be patients of the University of Alberta Upper Airway Dysfunction Clinic. This multi-disciplinary clinic includes, ortolaryngology, pediatric pulmonology, radiology, and orthodontics. No physical facilities from AHS are expected to be used.

3.0 * **Indicate if the proposed research has or will receive ethics approval from other Research Ethics Board or institution. Choose all that apply:**
Not Applicable

If OTHER, list the REB or Institution:
Name
There are no items to display

4.0 **Does this study involve pandemic or similar emergency health research?**
○ Yes ◉ **No**

If YES, are you the lead investigator for this pandemic study?
○ Yes ○ No

5.0 **If this application is closely linked to research previously approved by one of the University of Alberta REBs or has already received ethics approval from an external ethics review board***(s)*, **provide the HERO study number, REB name or other identifying information. Attach any external REB application and approval letter in Section 7.1.11 – Other Documents.**
Title: CBCT Oropharyngeal Airway Measurements in Maxillary

Transverse Deficiency
Approval #: Pro00019986

2.1 Study Objectives and Design

1.0 **Date that you expect to start working with human participants:**
9/1/2011

2.0 **Date that you expect to finish working with human participants, in other words, you will no longer be in contact with the research participants, including data verification and reporting back to the group or community:**
7/31/2013

3.0 * **Provide a lay summary of your proposed research suitable for the general public** *(restricted to 300 words)***. If the PI is not affiliated with the University of Alberta, Alberta Health Services or Covenant Health, please include institutional affiliation.**

Obstruction of the upper airway in children has been linked to many orthodontic and systemic health problems. Reported problems include altered growth of the face and skeleton, sleep disordered breathing, high blood pressure, changes to the heart muscle, behavioral problems, and lower grades in school. With timely diagnosis many symptoms could be preventable.

Orthodontists can play an important role as early detection of upper airway dysfunction. Traditionally orthodontists have used 2D profile x-rays to assess the airway, but research has demonstrated 2D x-rays are not reliable for diagnosing upper airway dysfunction. Instead, cone-beam computerized tomography (CBCT) - a relative low radiation dose 3D x-ray that is frequently used for a standard orthodontic radiographic examination - permits a non-invasive assessment of the upper airway.

In the present study the diagnostic ability of CBCT images will be compared against the currently most used tool, nasoendoscpy - an invasive technique that involves passing a camera through a child's nasal passage. Two common causes of upper airway dysfunction, enlarged adenoids and deviated nasal septum, will be assessed and compared between the two methods.

4.0 * **Provide a description of your research proposal including study objectives, background, scope, methods, procedures, etc)** *(restricted to 1000 words)***. Footnotes and references are not required and best not included here. Research methods questions in Section 5 will prompt additional questions and information.**

Objective

Examine the sensitivity and specificity of three dimentional imaging from cone-beam computerized tomography (CBCT) for diagnosing

adenoid hypertrophy and deviated nasal septum. Nasoendoscopy will be used as the gold standard comparison against CBCT images.

Rational

Provide orthodontists with a more accurate, non-invasive diagnostic tool for early detection nasopharyngeal airway dysfunction. Accurate and early diagnosis will greatly improve patient selection that require referral to ortolaryngology for possible airway surgery, and interventions due to early diagnosis may prevent altered craniofacial growth minimizing the need for later orthodontic treatment.

Background

Common potential sources of nasopharyngeal obstruction are adenoid hypertrophy, chronic rhinitis, and deviated nasal septum. Reports have associated upper airway constriction with mouth breathing and pediatric obstructive sleep apnea (POSA). The orthodontist should be prepared to manage both conditions with orthodontic therapy and/or appropriate otolaryngology referral.

Mouth breathing has been a proposed as a significant factor for altered craniofacial growth: narrow maxillary arch, posterior crossbite, long face height, anterior open bite and mandibular retrognathia. Each of these presentations are indications for orthodontic treatment that may be prevented by early intervention. POSA has been associated with many systemtic problems such as reduced growth, systemic and pulmonary hypertension, and ventricular hypertrophy. Psyco-social and quality of life consequences are also observed including hyperactivity, attention deficit and aggression, plus reduced grades in school have been reported to occur.

In addition to treating the malocclusions that result from airway dysfunction, orthodontists can play a vital role in early detection. Orthodontists may thus avoid or intercept the ensuing systemic health and quality of life consequences with appropriate referrals. Clinical history such as chronic snoring, breathing interruption during sleep, growth rate, tendency to fall asleep during the day, behavioral difficulties and chronic runny nose can all be identified by an orthodontist. In addition, orthodontic radiographs may also be used for accurately screening upper airway dysfunction.

Traditionally orthodontists used lateral cephalograms to evaluate adenoid size. A recent systematic review could not identify a reliable 2D assessment of the upper airway. Imaging of the nasal septum and internal dimension of the nasal passage is usually inadequate or unavailable. Therefore, cephalometric validity for evaluation of airway obstruction is questionable. Orthodontists need an alternative low risk, simple and valid diagnostic tool to evaluate potential upper airway constriction.

Cone-beam computerized tomography (CBCT) provides low cost, accessible and acceptably low radiation for 3D evaluation of craniofacial structures, both for orthodontic diagnosis and potentially for airway dysfunction screening. With manual sectioning, dimensions and volumes of the airway can be accurately measured. However,

diagnostic efficacy of CBCT airway imaging is not known.

Our objective is to evaluate the sensitivity and specificity of diagnosing upper airway constriction – specifically, adnenoid hypertrophy and deviated nasal septum – with CBCT imaging compared to nasoendoscopy.

Methods

CBCT diagnostic efficacy for adenoid hypertrophy and deviated nasal septum will be evaluated with a prospective diagnostic study. Subjects will be recruited from a tertiary referral center, the University of Alberta multi-disciplinary upper airway dysfunction clinic. Subjects included will be male and female patients age 8-15 with clinical suspiction of upper airway dysfunction, and/or craniofacial development concerns. Subjects with known syndromes, neurological disorders or previous treatment for airway obstruction will be excluded.

An orthodontist, and otolaryngologist will complete assessments of all patients. All subjects will undergo nasopharyngoscopy and CBCT imaging. CBCT images will be taken within one week of the endoscopy using an iCAT (12 inch field of view). Subjects will be seated in an upright position, and restraints used to ensure no movement during image acquisition. CBCT images will be reconstructed and stored in DICOM format for secondary processing. All CBCT and video endoscopy images will be coded for blinding and randomized for measurement.

Severity of airway obstruction will be determined from CBCT and video endoscopy images with a subjective 4 point scale as defined by Ysunza et al.[20] This method considers adenoidal hypertrophy, velum, and lateral pharyngeal walls at the velopharnygeal level. Patients classified as moderate or severe (Grades 3 or 4) will be considered pathologically obstructed. Deviated septum will also be diagnosed dichotomously; a reduction of cross-sectional area greater than 50% will be considered pathologic.

A pilot study will be performed with 10 CBCT and nasoendoscopy records. Results from the pilot study will be used to calculate the needed sample size with an anticipated $\alpha\lambda\pi\eta\alpha$=0.05 and $\beta\varepsilon\tau\alpha$=0.2.

The inter-observer reliability of diagnosing adenoid hypertrophy and nasal septum deviation will be evaluated using a team of 5 calibrated researchers. 2 dental radiologists and 1 orthodontist will complete diagnosis of adenoid hypertrophy and deviated nasal septum using CBCT images. Likewise, 2 otolaryngologists and 1 orthodontist will complete the diagnosis from nasoendoscopy videos. This arrangement of evaluators will permit intra-specialty agreement as well as inter-specialty agreement. Intra-specialty agreement (ex. ENT vs ENT diagnosis using nasoendoscopy) will be compared against published standards to ensure quality control.

CBCT Intra-observer reliability of the orthodontic practitioner will also be evaluated by having the same individual make repeated diagnosis of the same image. To minimize the risk of bias the

following procedures will be completed. 1) Each CBCT image will be evaluated twice with a minimum of 1 month between assessments. 2) The order of DICOM files will be randomized for each assessment to minimize. Kappa scores will be used to quantify intra-observer reliability.

A calibrated expert will independently complete assessments of the nasopharyngeal airway. CBCT diagnostic validity will be evaluated with sensitivity and specificity assessments. Receiver-operator characteristic analysis will be used to evaluate adequate cut-off points for sensitivity-sensitivity balance.

The ability of orthodontic practitioners to diagnose adenoid hypertrophy and deviated nasal septum will be compared against dental radiologists. Using the same CBCT images, a team of 5 participants – 2 dental radiologists and 3 orthodontists – will diagnose each patient for adenoid hypertrophy and deviated nasal septum. Of the 3 orthodontists, one will be a resident trained in airway assessment, and two will be practicing orthodontists who use CBCT imaging for their standard radiographic examination. Inter-specialty agreement will be calculated to evaluate the diagnostic ability of orthodontic practitioners.

5.0 **Describe procedures, treatment, or activities that are above or in addition to standard practices in this study area** *(eg. extra medical or health-related procedures, curriculum enhancements, extra follow-up, etc)*:
Current radiographic standard of care in orthodontics include the 2D lateral cephalogram and panorex radiographs. Although technically "above the standard practice" CBCT imaging is superior for research purposes because the same images can be used for both orthodontic treatment planning, plus additional evaluation of the hard and soft tissues and airway unavailable in 2D images. This imaging will be also used by the ENT specialists to refine their endoscopical diagnosis. Furthermore, 3D CBCT imaging has been increasingly growing as a replacement alternative for 2D radiographic assessment. Today many practicing orthodontists use CBCT exclusively as their radiographic imaging for orthodontic treatment planning.
In summary these patients will have already significant clinical signs of potential airway impairment. Therefore the extra radiation from the CBCT does provide extra information that will improve the diagnostic by both the ENT specialists and the orthodontists.

6.0 **If the proposed research is above minimal risk and is not funded via a competitive peer review grant or industry-sponsored clinical trial, the REB will require evidence of scientific review. Provide information about the review process and its results if appropriate.**
Department of Dentistry

7.0 **For clinical research only, describe any sub-studies associated with this application.**

3.1 Risk Assessment

1.0 * **Provide your assessment of the risks that may be associated with this research:**
Greater than Minimal Risk

2.0 * **Select all that might apply:**

Description of Potential Physical Risks and Discomforts

No	Participants might feel physical fatigue, e.g. sleep deprivation
No	Participants might feel physical stress, e.g. cardiovascular stress tests
Yes	Participants might sustain injury, infection, and intervention side-effects or complications
Yes	The physical risks will be greater than those encountered by the participants in everyday life

Potential Psychological, Emotional, Social and Other Risks and Discomforts

No	Participants might feel psychologically or emotionally stressed, demeaned, embarrassed, worried, anxious, scared or distressed, e.g. description of painful or traumatic events
No	Participants might feel psychological or mental fatigue, e.g intense concentration required
No	Participants might experience cultural or social risk, e.g. loss of privacy or status or damage to reputation
No	Participants might be exposed to economic or legal risk, for instance non-anonymized workplace surveys
No	The risks will be greater than those encountered by the participants in everyday life

3.0 * **Provide details of the risks and discomforts associated with the research, for instance, health cognitive or emotional factors, socio-economic status or physiological or health conditions:**
There are two sources of risk in the proposed study: 1) nasoendoscopy, 2) CBCT.
The patient can expect to feel discomfort during the endoscopy procedure. Pain may occur, but is usually mild. Risks associated with nasoendoscopy are possible injury to the nasal passage. While injury risk is low, a nose bleed that resolves within a 1-2 minutes would be the most common severity.
Risks associated with CBCT are those common to all radiology. The patient will experience no immediate discomfort. All risks are associated with theoretical long term consequences of radiation.
Risks to research subjects are identical to the risks of any individual requiring diagnostic testing for a similar medical history. The risks encountered by research subjects are identical to those encountered during the standard of care diagnostic procedures.

4.0 * **Describe how you will manage and minimize risks and discomforts, as well as mitigate harm:**
Regarding nasoendoscopy: Properly trained personal will perform the scoping, anesthetic spray will be administered to each patient prior to nasoendoscopy to minimize discomfort. If injury results, the patient will be monitored until the nose bleed resolves. ENT hospital support is available should the patient develop more significant side effects.

CBCT is a low-dose technique for 3D radiology, and as such minimizes the patients radiation risk while maximizing the anatomical information available in the radiography. The minimal radiation dose needed to acquire diagnostically reliable images will be used.

5.0 * **If your study has the potential to identify individuals that are upset, distressed, or disturbed, or individuals warranting medical attention, describe the arrangements made to try to assist these individuals. Explain if no arrangements have been made:**
Prior to nasoendoscopy, patients will be given the opportunity to calm themselves before proceeding.

3.2 Benefits Analysis

1.0 * **Describe any potential benefits of the proposed research to the participants. If there are no benefits, state this explicitly:**
Early and accurate diagnosis of upper airway dysfunction can permit treatment that may prevent altered craniofacial growth and avoid systemic health consequences. Early intervention of airway dysfunction may prevent the need for significant downstream treatment.

2.0 * **Describe the scientific and/or scholarly benefits of the proposed research:**
If CBCT can aid with early diagnosis thereby guiding early treatment, then there is significant potential for avoiding later physical suffering the consequences of sleep disordered breathing, and avoid the phsyco-social suffering associated with altered craniofacial development.

Early interventions resulting from early and accurate diagnosis could have significant cost savings by preventing potential hospital stays and avoiding costly orthodontic treatment, in addition to phsyco-social benefits of improved behavior and grades in school.

3.0 **Benefits/Risks Analysis: Describe the relationship of benefits to risk of participation in the research:**
The overall risk to the patient is very low relative to the current standard of care relating to upper airway dysfunction. The procedure with the greatest risk, nasoendoscopy, is the gold standard of care for diagnosing upper airway dysfunction, therefore all patients with similar symptoms would have this procedure. The CBCT radiograph is non-invasive and involves minimally greater radiation dose than traditional orthodontic radiographs. In fact, the difference in radiation between 2D and 3D is small enough that many clinicians use 3D over 2D as their standard practice.

4.1 Participant Information

1.0 * **Who are you studying? Describe the population that will be included in this study.**

Children age 6-15 with suspected upper airway problems will be studied. Examples of suspect medical histories may include: chronic allergies, sleep apnea, mouth breathing, altered craniofacial growth, suppressed systemic growth, difficulties concentrating, or poor grades in school.

2.0 * **Describe the inclusion criteria for participants (e.g. age range, health status, gender, etc.). Justify the inclusion criteria (e.g. safety, uniformity, research methodology, statistical requirement, etc)**

Included subjects will be age 6-15. All subjects within this age range are still growing, and therefore are both suseptable the consequences of pediatric airway dysfunction and likely to benifit from treatment.

3.0 **Describe and justify the exclusion criteria for participants:**

Subjects with known syndroms, neurological disorders, cancer, cleft lip / palate, or previous treatment for airway dysfunction will be excluded. Each of these traits has the ability to confound the data of interest.

4.0 * **Are there any recruitment activities for this study?**

(•) **Yes** ( ) No

Note: No means no direct contact with participants, chart reviews, secondary data, interaction, etc.

If NO, is this project a chart review or is a chart review part of this research project?

( ) Yes ( ) No

5.0 **Participants**

How many participants do you hope to recruit *(including controls, if applicable)*
30
Of these how many are controls, if applicable *(Possible answer: Half, Random, Unknown, or an estimate in numbers, etc).*
0
If this is a multi-site study, for instance a clinical trial, how many participants *(including controls, if applicable)* **are expected to be enrolled by all investigators at all sites in the entire study?**
0

6.0 **Justification for sample size:**
Eligible subjects identified between September 2011 to December 2012 will be accepted. The study is a diagnostic study, therefore no control group is needed. We anticipate 20-30 subjects will be recruited. More precise final number will be determined after an early study

analysis. No multi-site data is anticipated within the time frame of the study.

7.0 Does the research specifically target aboriginal groups or communities?

○ Yes ◉ **No**

4.3 Recruit Potential Participants

1.0 Recruitment

1.1 How will potential participants be identified? Outline how you will identify the people who will be approached for participation or screened for eligibility.
Potential subjects will be identified by referral from dentists or physicians. Referrals will be based on a medical history suspicious for upper airway dysfunction.

1.2 How will people obtain details about the research in order to make a decision about participating? Select all that apply:
Researchers will contact potential participants
Contact will be made through an third party or intermediary (including snowball sampling)

1.3 If appropriate, provide the locations where recruitment will occur *(e.g schools, shopping malls, clinics, etc.)*
Patients will be first refereed to the clinic as described above and will be then recruited directly in the University of Alberta Upper Airway Dysfunction clinic, a tertiary referral center.

2.0 Pre-Existing Relationships

2.1 Will potential participants be recruited through pre-existing relationships with researchers *(e.g. Will an instructor recruit students from his classes, or a physician recruit patients from her practice? Other examples may be employees, acquaintances, own children or family members, etc)***?**

◉ **Yes** ○ No

2.2 If YES, identify the relationship between the researchers and participants that could compromise the freedom to decline *(e.g. professor-student)***. How will you ensure that there is no undue pressure on the potential participants to agree to the study?**
Subjects recruited are patients of the University of Alberta Upper Airway Dysfunction Clinic, and therefore may be patients of the researchers.

3.0 Outline any other means by which participants could be identified, should additional participants be needed *(e.g. response to advertising such as flyers, posters, ads in newspapers, websites, email, listservs; pre-existing records or existing registries; physician or community organization referrals; longitudinal study, etc)*

Patients may be referred to the Upper Airway Dysfunction Clinic through community based orthodontists, ortolaryngologists, or pediatric pulminologists.

4.0 **Will your study involve any of the following** *(select all that apply)***?**
None of the above

4.4 Third Party or Intermediary Contact Methods

1.0 **If contact will be made through an intermediary** *(including snowball sampling)***, select one of the following:**
Intermediary provides potential participant's contact information to researchers WITHOUT participant's informed consent for release of contact information

2.0 **Explain why the intermediary is appropriate and describe what steps will be taken to ensure participation is voluntary:**
A community based physician or dentist properly trained to recognize upper airway dysfunction requiring multi-disciplinary treatment may refer a patient to the Upper Airway Dysfunction clinic. From within the clinic, subjects may be recruited for the study. Referred patients will have accompanying personal information and copies of records. Like all medical records, access will be restricted to approved team members and not be further distributed without the patients informed consent.

4.5 Informed Consent Determination

1.0 * **Describe who will provide informed consent for this study (select all that apply). Additional information on the informed consent process is available at:**
http://www.pre.ethics.gc.ca/eng/policy-politique/initiatives/tcps2-eptc2/chapter3-chapitre3/#toc03-intro
Third party consent will be sought

Provide justification for requesting a Waiver of Consent (Minimal risk only, additional guidance available at:
http://www.pre.ethics.gc.ca/eng/policy-politique/initiatives/tcps2-eptc2/chapter3-chapitre3/#toc03-1b
NA

2.0 **How is participant consent to be indicated and documented? Select all that apply:**
Signed consent form

Except for "Signed consent form" use only, explain how the study information will be communicated and participant consent will be documented. Provide details for EACH of the option selected above:
NA

NA

NA

3.0 Authorized Representative, Third Party Consent, Assent

3.1 Explain why participants lack capacity to give informed consent *(e.g. age, mental or physical condition, etc.).*
Subjects will be 6-15 years of age, and therefore unable to provide legal consent. Their primary care providers (likely parents) will provide the consent.

3.2 Will participants who lack capacity to give full informed consent be asked to give assent?
(•) **Yes** ( ) No

Provide details. IF applicable, attach a copy of assent form(s) in the Documentation section.
Assent will be requested from the subjects at the same time consent is requested from the subjects parents.

3.3 In cases where participants (re)gain capacity to give informed consent during the study, how will they be asked to provide consent on their own behalf?
Since the study is a cross-sectional diagnostic study, no subjects will gain the capacity to consent.

4.0 What assistance will be provided to participants, or those consenting on their behalf, who have special needs? *(E.g. non-English speakers, visually impaired, etc)***:**
Since all subjects are younger than 18, parents or legal guardians will be present for consultation and provide consent on behalf of study subjects. Non-english speaking families will be given the opportunity to have a translator present for consultation. Visual impairment should not restrict a patients ability to understand treatment plans.

5.0 * If at any time a participant wishes to withdraw, end, or modify their participation in the research or certain aspects of the research, describe how their participation would be ended or changed.
A patient can choose to decline the diagnostic procedures in the Upper Airway Dysfunction clinic at any time before starting. Since all information collected for the purpose of research is also absolutely vital for proper diagnosis and treatment planning, a patient cannot choose to refuse participation in certain aspects of data collection without also declining further treatment.

6.0 Describe the circumstances and limitations of data withdrawal from the study, including the last point at which it can be done:
All data will be collected at the same time. Since data is cross-sectional, it is impossible to define a "last point of withdrawal".

7.0 Will this study involve any group(s) where non-participants are present? For example, classroom research might involve groups which include participants and non-participants.
( ) Yes (•) **No**

5.1 Research Methods and Procedures

Some research methods prompt specific ethic issues. The methods listed below have additional questions associated with them in this application. If your research does not involve any of the methods listed below, ensure that your proposed research is adequately described in Section 2.0: Study Objectives and Design or attach documents in Section 7.0 if necessary.

1.0 * **This study will involve the following** *(select all that apply)*
The list only includes categories that trigger additional page(s) for an online application. For any other methods or procedures, please indicate and describe in your research proposal in the Study Summary, or provide in an attachment:
Radiation: Any test or procedure that may involve exposure to radiation (including screening chest x-ray)

2.0 **Is this study a Clinical trial? (Any investigation involving participants that evaluates the effects of one or more health-related interventions on health outcomes?**
○ Yes ◉ **No**

3.0 **If you are using any tests in this study diagnostically, indicate the member(s) of the study team who will administer the measures/instruments:**

Test Name	Test Administrator	Organization	Administrator's Qualification

There are no items to display

4.0 **If any test results could be interpreted diagnostically, how will these be reported back to the participants?**
Diagnostic data will be evaluated by orthodontists, radiologists, otolaryngologists, and pediatric pulmonologists. After multi-disciplinary diagnoses and treatment plans have been formed, a consultation will be complete with the patient to inform them of the relevant diagnoses and treatment plans.

5.14 Radiation Safety

1.0 **Will your research involve:**
There are no items to display

"If you take part in this research, you will be exposed to a very small amount of radiation. The risk from this amount of radiation has been categorized by the Radiation Safety Committee as 'very low'."

Note: If you have checked either of these boxes, a separate application to the Radiation Safety Committee (RSC) for approval is not usually required.

2.0 **Will your research involve exposure of subjects aged 0-17 years to any amount of ionizing radiation?**
◉ **Yes** ○ No

Regardless of how little radiation is involved, this requires separate application to the Radiation Safety Committee (RSC) for approval. Please complete section 3.0 and contact the committee as indicated below.

3.0 **Will your research involve any of the following at screening, baseline or follow-up?** *(Check all that apply)*
X-rays of the skull, facial bones, neck, spine, thorax, abdomen, pelvis or hip

Note: if you checked any box in section 3.0, you need to apply for RSC approval.

To apply for RSC approval, e-mail a copy of the complete research protocol, including patient information sheet, to: radnsfty@ualberta.ca

In most cases, RSC approval will be issued in 1-2 days, unless otherwise notified. Some rewording of the patient information sheet is often required. Protocol amendment is rarely necessary.

For further information, contact the RSC at:

Dr. R. Lambert
Chair, Alberta Health Services/University of Alberta Regional Radiation Safety Committee
2A2.18 WMC, UAH Site
Ph. 407-8223, Fax 407-3853,
E-mail: radnsfty@ualberta.ca

6.1 Data Collection

1.0 * **Will the researcher or study team be able to identify any of the participants at any stage of the study?**
(•) **Yes** ( ) No

2.0 **Will participants be recruited or their data be collected from Alberta Health Services or Covenant Health or data custodian as defined in the Alberta Health Information Act?**
(•) **Yes** ( ) No

Important: Research involving health information must be reviewed by the Health Research Ethics Board.

3.0 **Primary/raw data collected will be** *(check all that apply)*:
Indirectly identifying information - the information can reasonably be expected to identify an individual through a combination of indirect identifers (eg date of birth, place of residence, photo or unique personal characteristics, etc)
All personal identifying information removed (anonymized)

4.0 **If this study involves secondary use of data, list all original**

sources:
N/A

5.0 **In research where total anonymity and confidentiality is sought but cannot be guaranteed** *(eg. where participants talk in a group)* **how will confidentiality be achieved?**
N/A

6.2 Data Identifiers

1.0 * **Personal Identifiers:** will you be collecting - at any time during the study, including recruitment - any of the following *(check all that apply)*:
Surname and First Name
Initials
Address
Full Postal Code
First 3 digits of postal code
Telephone Number
Fax Number
Full Face Photograph or Other Recording
Full Date of Birth
Year of Birth
Age at time of data collection

If OTHER, please describe:

2.0 **Will you be collecting - at any time of the study, including recruitment of participants - any of the following** *(check all that apply)*:
Health Care Number
Medical Record Number

If OTHER, please describe:

3.0 * **If you are collecting any of the above, provide a comprehensive rationale to explain why it is necessary to collect this information:**
Patient name, contact information, health care number, etc will be collected as part of the patient's treatment record. This data will not be used in the data analysis or publication of results.

4.0 **If identifying information will be removed at some point, when and how will this be done?**
Identifying information will be removed and coded immediately after collection.

5.0 * **Specify what identifiable information will be RETAINED once data collection is complete, and explain why retention is necessary. Include the retention of master lists that link participant identifiers with de-identified data:**
All information will be retained on a secure, encrypted server from the

department of dentistry. In addition, the coding master list will be stored under a different file designation from the diagnostic data.

6.0 **If applicable, describe your plans to link the data in this study with data associated with other studies (e.g within a data repository) or with data belongong to another organization:**
There are no plans to link data with another organization.

6.3 Data Confidentiality and Privacy

1.0 * **How will confidentiality of the data be maintained? Describe how the identity of participants will be protected both during and after research.**
Patient records are saved on a secure server in encrypted files. All computers accessing patient records require password log in. Access to patient records are restricted to approved personnel.

2.0 **How will the principal investigator ensure that all study personnel are aware of their responsibilities concerning participants' privacy and the confidentiality of their information?**
All personnel with access to subject data have been properly trained to protect patient identity and medical history confidentiality.

3.0 **External Data Access**

* **3.1 Will identifiable data be transferred or made available to persons or agencies outside the research team?**
○ Yes ◉ **No**

3.2 If YES, describe in detail what identifiable information will be released, to whom, why they need access, and under what conditions? What safeguards will be used to protect the identity of subjects and the privacy of their data.

3.3 Provide details if identifiable data will be leaving the institution, province, or country *(eg. member of research team is located in another institution or country, etc.)*
All researchers are based at the University of Alberta.

6.4 Data Storage, Retention, and Disposal

1.0 * **Describe how research data will be stored, e.g. digital files, hard copies, audio recordings, other. Specify the physical location and how it will be secured to protect confidentiality and privacy.** (For example, study documents must be kept in a locked filing cabinet and computer files are encrypted, etc.)
Active patient records are saved as encrypted files on a secure server located in the University of Alberta Dentistry/Pharmacy Centre.

Archived data will be stored on a secure server with encrypted files.

2.0 * **University policy requires that you keep your data for a minimum of 5 years following completion of the study but there is no limit on data retention. Specify any plans for future use of the data. If the data will become part of a data repository or if this study involves the creation of a research database or registry for future research use, please provide details.**
Data collected from this study may become part of a research database for future use. All subjects enlisted for the research project outlined in this proposal will have the opportunity for treatment from the appropriate specialist in the multi-disciplinary team. Patients choosing treatment will be followed longitudinally. The goal of creating the database will be to more accurately diagnose the problems, discover how to best treat, and better understand the effects of upper airway dysfunction on craniofacial growth and systemic health. It is expected that any future use of the collected data will have to be previously approved by the HREB.

3.0 **If you plan to destroy your data, describe when and how this will be done? Indicate your plans for the destruction of the identifiers at the earliest opportunity consistent with the conduct of the research and/or clinical needs:**
After the study is complete, all coding will be removed. Identifiers will be removed as soon as data analysis has been completed. Relevant data will be stored with the subjects medical record.

7.1 Documentation

Add documents in this section according to the headers. Use Item 11.0 "Other Documents" for any material not specifically mentioned below.

Sample templates are available in the HERO Home Page in the **Forms and Templates**, or by clicking HERE.

1.0 **Recruitment Materials:**

Document Name	Version	Date	Description
There are no items to display			

2.0 **Letter of Initial Contact:**

Document Name	Version	Date	Description
Letter to Orthodontists v1 | History	0.01	8/1/2011 12:16 PM	

3.0 **Informed Consent / Information Document(s):**

3.1 What is the reading level of the Informed Consent Form(s):

3.2 Informed Consent Form(s)/Information Document(s):

Document Name	Version	Date	Description
Parent Information Sheet V4.docx | History	0.06	8/25/2011 9:21 AM	
Pediatric Information Sheet and Assent Form v3 | History	0.02	8/24/2011 9:12 PM	

4.0 Assent Forms:

Document Name	Version	Date	Description
Parent Consent Form v3.docx | History	0.04	8/24/2011 12:08 PM	

5.0 Questionnaires, Cover Letters, Surveys, Tests, Interview Scripts, etc.:

Document Name	Version	Date	Description
There are no items to display			

6.0 Protocol:

Document Name	Version	Date	Description
There are no items to display			

7.0 Investigator Brochures/Product Monographs *(Clinical Applications only)*:

Document Name	Version	Date	Description
There are no items to display			

8.0 Health Canada No Objection Letter *(NOL)*:

Document Name	Version	Date	Description
There are no items to display			

9.0 Confidentiality Agreement:

Document Name	Version	Date	Description
There are no items to display			

10.0 Conflict of Interest:

Document Name	Version	Date	Description
There are no items to display			

11.0 Other Documents:

For example, Study Budget, Course Outline, or other documents not mentioned above

Document Name	Version	Date	Description
There are no items to display			

Final Page

You have completed your ethics application! Please select "Exit" to go to your study workspace.

This action will NOT SUBMIT the application for review.

Only the Study Investigator can submit an application to the REB by selecting the "SUBMIT STUDY" button in My Activities for this Study ID:Pro00020649.

You may track the ongoing status of this application via the study workspace.

Please contact the REB Administrator with any questions or concerns.

AHS ADMINISTRATIVE APPROVAL FOR RESEARCH

Northern Alberta Clinical Trials and Research Centre
Research Administration
1800 College Plaza
8215 - 112 Street NW
Edmonton, AB T6G 2C8
www.nactrc.ca

Protocol Acronym: ____ **Protocol #:** ____ **HERO #:** Pro00020649 **Ethics Approved:** Aug 31, 2011

Protocol Title:
Evaluation of Cone-Beam Computerized Tomography (CBCT) for Diagnosis of Adenoid Hypertrophy an Deviated Nasal Septum

Principal Investigator:	Dr. Carlos Flores Mir	**Funding Agency:**	Internal Funding
Faculty:	Medicine & Dentistry	**Funding Type:**	Investigator-Initiated/Internal and/or Contingency Funding
Department:	Dentistry & Dental Hygiene	**Overhead Rate:**	0%

AHS Operational Approvals:

12987: Stollery - ENT Clinic

Comments:

AHS Admin File #:	30775
Approved:	Sep 30, 2011
Approved By:	Carlos Miranda NACTRC Research Administration On Behalf of Alberta Health Services

Approval Form - HIA Consent

Date:	August 31, 2011
Principal Investigator:	Carlos Flores Mir
Study ID:	Pro00020649
Study Title:	Evaluation of Cone-beam Computerized Tomography (CBCT) for Diagnosis of Adenoid Hypertrophy an Deviated Nasal Septum
Approval Expiry Date:	August 29, 2012
Date of Informed Consent:	Approval Date / Approved Document 8/31/2011 Pediatric Information Sheet and Assent Form v3 8/31/2011 Parent Information Sheet V4.docx
Funding/Sponsor :	McIntyre Funds

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 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 (August 29, 2012), 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).

Appendix E: Parent / Guardian Research Information Sheet

INFORMATION SHEET

Title of Research Study **CBCT imaging for upper airway dysfunction**

Principal Investigator(s): Dr Carlos Flores-Mir

Co-Investigator(s): Dr Michael Major, Dr Hamdy El-Hakim, Dr Manisha Witmans, Dr Paul Major

Purpose: To evaluate the usefulness of CBCT (3D orthodontic x-rays) for diagnosing deviated nasal septum (a narrow bone down the middle of the nose) and enlarged adenoids (a tonsil like tissue at the back of the nose).

Background: Your child has suspected nose breathing and orthodontic problems that may be related. In order to properly diagnose these problems your child requires nasoendoscopy (small camera inserted in the nose to identify blockage in the nasal airway) and orthodontic x-rays. For this study we would like your child to have a single 3D x-ray instead of multiple 2D x-rays for your orthodontic records. In addition to helping us understand your child's orthodontic problems, the 3D x-ray could tell us more about your child's nose breathing problems too. Approximately 20-30 people with airway dysfunction (breathing problems) will take part in this study.

Procedures: If you agree to take part, your child will come to the orthodontic office one time for orthodontic x-ray's and to the hospital one time for nasoendoscopy on the same day. The information collected will be used to decide what treatment your child will require. Everyone in the study will have the same procedures.

Benefits: The information collected will help us diagnose your child's problems, and may help us diagnosis similar problems in future patients more quickly and accurately.

Risks: Your child will not feel the x-ray. The radiation is near the same as the usual series of 2D x-rays. The nasoendoscopy may feel uncomfortable, cause a momentarily nosebleed, or hurt for a day or two. But the nasoendoscopy is essential for proper diagnosis and needed even if you were not part of the study. If your nose keeps hurting for more than 2 days or you have more nosebleeds, take your child to their doctor.

Withdrawa:l Since the x-ray and nasoendoscopy is a one-time event there is no opportunity to quit from the study. Both are necessary for us to properly treat your airway and orthodontic problems.

Confidentiality: No one except you, your child, and research team 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 or presentation based on study data will not identify you by any means.

Additional Contacts:
If you have questions regarding the study you can contact to Dr. Flores at 780-492-7409. If you have questions regarding the study ethics or you want to express concerns regarding the process you can contact the University of Alberta Ethics Office at XXX-XXX-XXXX.

Appendix F: Parent / Guardian Research Consent Form

Consent to Research Participation

Part 1 (to be completed by the Principal Investigator):

Title of Project: *CBCT Imaging for Diagnosis of Upper Airway Dysfunction*

Investigator(s): Dr Michael Major, Dr Carlos Flores-Mir, Dr Hamdy El-Hakim, Dr Manisha Witmans, Dr Paul Major

Part 2 (to be completed by the research subject):

Do you understand that you have 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

Have you had an opportunity to ask questions and discuss this study?
Do you understand that you are free to refuse to participate or withdraw from the study at any time? You do not have to give a reason and it will not affect your care. *(Use wording appropriate to your subject group)*

Has the issue of confidentiality been explained to you? Do you understand who will have access to your records?

Do you want the investigator(s) to inform your family doctor that you are participating in this research study? If so, please provide your doctor's name: _____ *(N.B. This question is optional).*

This study was explained to me by: _____

I agree to take part in this study.

_____	_____	_____
Signature of Research Participant	Date	Witness
_____		_____
Printed Name		Printed Name

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

THE INFORMATION SHEET MUST BE ATTACHED TO THIS CONSENT FORM AND A COPY GIVEN TO THE RESEARCH SUBJECT

Appendix F: Child Research Assent Form

INFORMATION SHEET AND ASSENT FORM

Title of Research Study **CBCT imaging for upper airway dysfunction**

Principal Investigator(s): Dr Carlos Flores-Mir

Co-Investigator(s): Dr Michael Major, Dr Hamdy El-Hakim, Dr Manisha Witmans, Dr Paul Major

We suspect you have upper airway and orthodontic problems. You require nasoendoscopy (small camera inserted in your nose to see your nasal airway) and orthodontic x-rays for proper diagnosis. For this study we would like you to have a single 3D x-ray instead of multiple 2D x-rays for your orthodontic radiographs. In addition to helping us understand your orthodontic problems, the 3D x-ray tell us more about your upper airway problems too. Approximately 20-30 people with airway dysfunction will take part in this study.

What will you have to do?: If you and your parents agree to take part, we will ask you to come to our office one time for orthodontic x-ray's and nasoendoscopy before we decide what treatment you will require. Everyone in the study will have the same procedures as you.

Will it help?: The information collected will help us diagnose your problems, and may help us diagnosis similar problems in future patients more quickly and accurately.

Will it hurt?: You will not feel the 3D x-ray. The radiation is near the same as the usual series of 2D x-rays. The nasoendoscopy may feel uncomfortable, cause a momentarily nose bleed, or hurt for a day or two. But due to your upper airway problems, you would need to have the nasoendoscopy even if you were not part of the study. 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.

Can you quit?: Since the x-ray and nasoendoscopy is a one-time event there is no opportunity to quit from the study. Both are necessary for us to properly treat your airway and orthodontic problems.

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 based on study data will not identify you by any means. All patient data without personal identifiers will be combined for study purposes.

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.

Do you have more questions? You can ask your mom or dad about anything you don't understand.
If you have questions regarding the study you can contact to Dr. Flores at 780-492-7409. If you have questions regarding the study ethics or you want to express concerns regarding the process you can contact the University of Alberta Ethics Office at XXX-XXX-XXXX.

I agree to take part in the study.

_____	_____
signature of research participant	date
_____	_____
signature of witness	date
_____	_____
signature of investigator	date