



401 N. Lindbergh Blvd.
St. Louis, MO 63141
Tel.: 314.993.1700, #546
Toll Free: 800.424.2841, #546
Fax: 800.708.1364
Cell: 314.283.1983

Send via email to: jbode@aaortho.org and cyoung@aaortho.org

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Type of Award, e.g., Orthodontic Faculty Development Fellowship Award, Postdoctoral Fellowship Award, Biomedical Research Award, Center Award, Educational Innovation Award, Program Award, **Research Aid Award**

Name(s) of Principal Investigator(s) **Cassandra Campbell, Snehlata Oberoi (mentor)**

Institution **University of California San Francisco**

Title of Project **Rapid Maxillary Expansion and Protraction alleviates Obstructive Sleep Apnea in Non syndromic children with Cleft Palate**

Period of AAOF Support (e.g. 07-01-18 to 06-30-19): **07-01-17- 06-30-18**

Amount of Funding **\$5,000**

Summary/Abstract

Detailed results and inferences:

1. If the work has been published please attach a pdf of manuscript OR

Please see attached thesis.

2. Describe in detail the results of your study. The intent is to share the knowledge you have generated with the AAOF and orthodontic community specifically and other who may benefit from your study. Table, Figures, Statistical Analysis and interpretation of results should be included.

Response to the following questions:

1. Were the original, specific aims of the proposal realized? **Yes**
2. Were the results published? **Not yet**
 - a. If so, cite reference/s for publication/s including titles, dates, author or co-authors, journal, issue and page numbers
 - b. Was AAOF support acknowledged?
 - c. If not, are there plans to publish? If not, why not?
3. Have the results of this proposal been presented? **Yes at the 2017 PCSO Annual Session**
 - a. If so, list titles, author or co-authors of these presentation/s, year and locations
**Cassandra Campbell, Gerald Nelson, Gwynne Church, Snehlata Oberoi
2017 PCSO Annual Session**
 - b. Was AAOF support acknowledged? **Yes**
 - c. If not, are there plans to do so? If not, why not?
3. To what extent have you used, or how do you intend to use, AAOF funding to further your career?

The Resident Aid Award from the AAOF has allowed us to study the effect of RME on obstructive sleep apnea in children with non-syndromic cleft palate. Support has allowed us to perform the study with specialized software from 3DMD called Vultus which we were able to purchase with the funds we received. Additionally, Cassandra Campbell was able to present her work at the PCSO Annual session and was able to use some funds for travel. We were also able get statistical support with the funding as well. Cassandra is now in Private practice in San Antonio and plans to work with children with cleft lip and palate and join the craniofacial team. This research has allowed her to gain experience in the treatment of children with cleft lip and palate and she will continue to use her experience in her career. This also allowed her to appreciate the level of support from the AAOF for residents entering a career in Orthodontics, for which we both are grateful.

We thank the AAOF for the continued support that has enabled us to shed more light on sleep apnea in children with cleft palate.

Respectfully submitted,
Snehlata Oberoi

Rapid Maxillary Expansion and Protraction Alleviates Obstructive
Sleep Apnea in Non-Syndromic Children with Cleft Palate

by

Cassandra Campbell DDS

THESIS

Submitted in partial satisfaction of the requirements for the degree of

MASTER OF SCIENCE

in

Oral and Craniofacial Sciences

in the

GRADUATE DIVISION

of the

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

Approved:

Chair

Inelata Oberoi

G. Chund

Geoff Nelson 05-06-2018

Committee in Charge

ACKNOWLEDGEMENTS

I would like to thank Dr. Sneha Oberoi for giving me this opportunity to work with her on this study and for keeping my research progress on track. I also would like to thank her for pushing me to work harder on my thesis and her mentorship all along. I admire her dedication to treating children and adults with craniofacial anomalies and cleft palate and training the residents to get some experience to do the same.

I would like to thank Dr. Gwynne Church for her guidance on this project, and for sharing her vast expertise on pediatric sleep disorders. I thank her for the opportunity to work on this study.

I would like to thank Dr. Gerald Nelson for his valuable advice on all things related to clinical orthodontics, and his mentorship throughout these four years.

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Rapid Maxillary Expansion and Maxillary Protraction Alleviates Obstructive Sleep Apnea in Non-Syndromic Children with Cleft Palate

Cassandra Campbell DDS

Background and Objective: Cleft palate with or without cleft lip (CP/L) is commonly associated with obstructive sleep apnea (OSA), but few studies exist which evaluate the presence of OSA in these children. Individuals with CP/L frequently suffer from severe maxillary constriction, an anatomical characteristic frequently found in OSA individuals. Rapid maxillary expansion (RME) is an orthodontic treatment approach that increases maxillary skeletal dimensions via expansion at the mid-palatal suture. This effect has been shown to reduce nasal airway resistance in previous studies, suggesting the use of RME as a potential treatment modality for pediatric OSA. However, Children with CP/L have a comparatively more complex etiology of upper airway obstruction and the efficacy of RME for treating OSA in individuals with CP/L has not been evaluated.

Materials and Methods: Twenty-four subjects between 6-12 years old with cleft palate with or without cleft lip requiring maxillary palatal expansion prior to alveolar bone grafting were recruited prospectively. Validated 22- item pediatric sleep questionnaires (PSQ) were given pre- and post-treatment with RME and were used to assess the risk of OSA in the patients. Cone beam computed tomography (CBCT) data was utilized to evaluate minimum cross sectional area using 3dMDvultus software (Atlanta, U.S.A).

Results: The volumetric data, as well as standard lateral cephalogram and transverse measurements were related to the scores on the PSQs. 29.2% of the recruited subjects met criteria for OSA on their pre-treatment PSQs, and those with OSA had a significant decrease in their scores post-treatment. The Minimal Cross Section of the airway

(MCA), lateral cephalograms and transverse measurements did not correlate with the PSQ scores.

Conclusions: Almost 30% of the pediatric subjects with cleft palate with or without cleft lip in our study were at high risk for OSA prior to orthodontic treatment, approximately 10 – 20 times the reported prevalence in the general pediatric population. RME and maxillary protraction treatment appears to improve symptoms of sleep disordered breathing in young subjects with cleft palate with or without cleft lip. Other than pediatric sleep questionnaires, the airway measurements from the three-dimensional imaging and lateral cephalograms did not appear to correlate with the pediatric sleep questionnaires and the patient's risk for obstructive sleep apnea.

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Chapter 1. Introduction

Cleft palate with/without cleft lip are common disorders, with an incidence of 1 in 680 live births in the United States each year and 0.69-2.51 per 1000 births worldwide.¹⁻

⁴ Cleft lip results from failure of the medial nasal prominence to contact or to maintain contact with the maxillary prominences, and therefore constitutes a disruption of normal development.⁴ Cleft lip and cleft palate are etiologically distinct. Cleft palate results from failure of the palatine shelves to fuse.³ This failure of the palatine shelves to fuse results in abnormalities in the final conformation and function of the upper airway. Common comorbidities associated with non-syndromic cleft palate with or without cleft lip include feeding intolerance, speech disorders, and obstructive sleep apnea.⁴

Obstructive sleep apnea affects 1-5% of children in the United States⁵ and is associated with serious neurocognitive and cardiovascular morbidity, systemic inflammation, and increased health care utilization. Treatment has been shown to decrease neurocognitive sequelae such as poor academic performance⁶ and attention deficit hyperactivity disorder,⁷ to improve right and left ventricular ejection fractions,⁸ and to decrease biomarkers of inflammation, such as c-reactive protein.⁹ Unfortunately, obstructive sleep apnea in children remains underdiagnosed. Furthermore, the prevalence of obstructive sleep apnea in non-syndromic children with cleft palate with/without cleft lip is estimated to be between 20-30%, 10-20 times the prevalence of obstructive sleep apnea in the general population.¹⁰

The gold standard for a diagnosis of obstructive sleep is an overnight polysomnographic evaluation which monitors sleep state and provides measurements of cardiac and respiratory functions like mean oxygen saturation, desaturation index,

total sleep time, and hypopnea index. These measurements are compared to the normal parameters of gas exchange. The apnea hypopnea index, or AHI, is the number of complete cessations (apnea) and partial obstructions (hypopnea) of breathing per hour divided by total sleep time. These events must last for longer than 10 seconds and partial obstructions must accompany arousal from sleep or decreases of three to four percent in blood oxygen levels. AHI is used to quantify the severity of obstructive sleep apnea. Pediatric standards consider an AHI below 1.5 to be normal, 1.5-5 to be mild OSA, 5-20 to be moderate to severe OSA, and an AHI of 20 or greater to be severely abnormal. Pediatric sleep questionnaires (PSQs) are another method for evaluating OSA in children. Although polysomnograms are still the gold standard for diagnosing OSA, they are cost and time prohibitive. PSQ scales are validated for clinical practice against polysomnography and adenotonsillectomy outcomes. The PSQ scale was developed at the University of Michigan (Regents of the University of Michigan 2006), and has a high sensitivity and specificity of 83% and 87% respectively for OSA prediction.

There are few studies that have evaluated the prevalence of obstructive sleep apnea in non-syndromic children with cleft palate with or without cleft lip. The prevalence is estimated to be between 20-30%, 10-20 times the prevalence of obstructive sleep apnea in the general, non-cleft, population.¹⁻³ Upper airway narrowing, both anatomic and physiologic, is a well-recognized risk factor for obstructive sleep apnea. The current view is that adenotonsillar hypertrophy is the major cause of sleep-disordered breathing in otherwise normal healthy children. In children with craniofacial deformities, upper airway obstruction is almost always multifactorial, and not primarily

related to adenoidal or tonsillar hypertrophy.^{11,12} The upper airway obstruction may occur at several levels, including the nose, nasopharynx, and palate/oropharynx.¹ All maxillary dimensions are smaller in individuals with a history of cleft, resulting in mid-face hypoplasia compared to individuals without a cleft.⁴ Maxillary constriction is associated with an increased risk for obstructive sleep apnea,¹³ and patients with obstructive sleep apnea have greater maxillary constriction compared to controls.¹⁴⁻¹⁶

Because patients with cleft palate with or without cleft lip have maxillary constriction, they are at higher risk for persistent obstructive sleep apnea post adenotonsillectomy. One study has found that up to 30% of patients with cleft palate with or without cleft lip had residual obstructive sleep apnea after adenotonsillectomy,¹⁷ as opposed to approximately 17% in otherwise normal children.¹⁸ Therefore, other treatment options for children with clefts and obstructive sleep apnea are needed. Adenotonsillectomy and continuous positive airway pressure (CPAP) have been the primary treatment modalities for children who suffer from obstructive sleep apnea. However, evidence suggests adenotonsillectomy is less effective in cleft patients, and both treatment modalities are invasive and ineffective at fully correcting obstructive sleep apnea. Minimally invasive treatment options for children who suffer from airway constriction issues, like the common orthodontic intervention of rapid maxillary expansion, have recently garnered significant interest in the medical and dental community. A meta-analysis reviewing literature on the effects of rapid maxillary expansion on obstructive sleep apnea in 2016 found a significant decrease in AHI after rapid maxillary expansion in children with obstructive sleep apnea, and suggests that

the treatment of rapid maxillary expansion may contribute towards diminishing obstructive sleep apnea in this patient population.³²

Maxillary expansion can be achieved surgically or orthodontically, and is indicated for individuals with bilateral crossbite and maxillary constriction.¹⁹ Rapid maxillary expansion (RME) refers to orthodontic expansion whereby an expander is cemented to the premolars and upper molar teeth, and regularly activated, opening the maxillary mid-palatal suture by distraction osteogenesis. Rapid maxillary expansion is effective in children and adolescents prior to bone maturation and closure of the intermaxillary suture, which occurs around 15 years of age.²⁰

Rapid maxillary expansion improves the quality of nasal respiration by decreasing nasal resistance and increasing the width and volume of the maxillary dental arch. Increasing the dimensions of the maxillary dental arch allows advancement of tongue position and facilitates proper lip seal when the mouth is closed. A subsequent increase in the oropharyngeal space follows the improved tongue position.³² While a decrease in minimum cross sectional area and oropharyngeal volume has not been demonstrated in cleft palate patients with CBCT analysis, studies have demonstrated nasal airway restriction in this patient population.²⁷ Furthermore, after rapid maxillary expansion, CBCT analysis has shown significant increase in the cross-sectional area of the upper airway at the posterior nasal spine to basion level.²⁸ A study was performed in 2011 that enrolled ten children with dental malocclusions and performed polysomnograms before orthodontic treatment and 12 and 24 months after rapid maxillary expansion. Twelve months after rapid maxillary expansion treatment, the apnea hypopnea index (AHI) decreased and the clinical symptoms had resolved, while

24 months after the end of the treatment no significant changes in the AHI or in other variables were observed. These results suggest that rapid maxillary expansion may be an effective treatment option for young patients with malocclusion and obstructive sleep apnea.²³

Besides transverse deficiency, another significant consideration in young patients with cleft palate is the effect maxillary retrusion has on the airway. Treatment for this patient population often includes both rapid maxillary expansion and maxillary protraction. Maxillary protraction is achieved through a maxillary protraction appliance, more commonly referred to as a reverse-pull headgear or a protraction facemask. It is reported that patients with mandibular retrognathism treated with mandibular advancement experience an increase in the dimensions of their oropharyngeal airway³³. This holds true in the non-growing patient treated with mandibular advancement surgery or with the growing patient treated with a functional appliance. It seems reasonable to expect that protraction of the maxilla in growing Class III patients with maxillary hypoplasia would also improve airway dimensions, and a systematic review performed in February of 2018 suggested that when this patient population is treated with maxillary protraction appliances their post-palatal and nasopharyngeal airway dimensions are increased. Specifically, the results indicated that the smallest upper airway width as measured from the posterior pharyngeal wall to the soft palate (known as McNamara's upper pharynx dimension) increased and were stable at long-term follow up. McNamara's lower pharynx dimension showed less change³³. This supports the notion that craniofacial anatomic factors are highly related to upper airway dimensions. Along with stimulating forward growth of the maxilla, maxillary protraction

appliances cause counterclockwise rotation of the palatal plane and subsequently clockwise rotation of the mandible. This rotation of the palatal plane brings the posterior nasal spine forward and contributes to the increase in the post-palatal airway dimension, while the anterior displacement of the maxilla would have positive effects on the nasopharyngeal airway dimensions. Given the improvement in these dimensions of airway space after treatment with a maxillary protraction appliance, these patients may have a reduced risk of Obstructive Sleep Apnea.³³

While the efficacy of RME with maxillary protraction for treating OSA in non-syndromic cleft palate with or without cleft lip has not previously been described, rapid maxillary expansion and maxillary protraction may be an effective and non-invasive treatment of pediatric obstructive sleep apnea in children who have either residual obstructive sleep apnea after tonsillectomy, or who are not good candidates for tonsillectomy.^{13, 21-23}

This study had three specific aims: 1) to determine the prevalence of sleep-disordered breathing in children with cleft palate with or without cleft lip prescribed RME by an orthodontist by using a validated pediatric sleep questionnaires, 2) to evaluate changes in pediatric sleep questionnaire scores before and after RME with maxillary protraction, and 3) to determine if volumetric data from the cone beam CT pre and post-RME, lateral ceph measurements and transverse analysis correlates with the pediatric sleep questionnaire scores.

The following null hypothesis was tested:

- The prevalence of sleep-disordered breathing in children with cleft palate with or without cleft lip presenting for orthodontic phase I treatment is not increased compared to the general pediatric population as determined by validated pediatric sleep questionnaires.
- The subject's pediatric sleep questionnaire scores do not decrease after treatment with RME and maxillary protraction.
- Volumetric data from the cone beam CT pre- and post-RME, lateral cephalogram measurements and transverse analysis do not correlate with the pediatric sleep questionnaire scores.

Chapter 2. Materials and Methods

CHR approval was obtained for this study from UCSF institutional review board (CHR #14-14246). Twenty-four non-syndromic patients with cleft lip and/or palate between the ages of 6-12 years were recruited in this study. Participation in this study was voluntary, and included parental informed consent as well as patient assent to collection and use of their data prior to inclusion. Our inclusion criteria were children between the ages of 6-12 years with cleft palate with or without cleft lip who had a posterior cross bite, and required maxillary palatal expansion (RME) prior to alveolar bone grafting.

Exclusion criteria: Our exclusion criteria were very specific: individuals below the age of 6 years and above the age of 12 years, obesity with BMI > 85 percentile for age, neuromuscular disease, chronic lung disease with an oxygen requirement, patients with known obstructive sleep apnea (OSA) who are treated with non-invasive ventilation therapy or who will be having surgical intervention for the OSA during the study period, genetic syndromes and severe sleep apnea as defined by polysomnographic criteria with an apnea hypopnea index (AHI) score of more than 30 events per hour, an obstructive apnea index (OAI) score of more than 20 events per hour, or arterial oxyhemoglobin saturation of less than 90% for 2% or more of total sleep. These children would need an immediate evaluation by a sleep specialist for possible adenotonsillectomy or non-invasive positive pressure ventilation during sleep.

RME, cone beam CT (CBCT) scanning, and lateral cephalograms were all performed per the current standards within the UCSF Division of Orthodontics and Pediatric Pulmonary and Sleep Medicine. We used a validated pediatric sleep

questionnaire (PSQ) (Regents of the University of Michigan 2006) administered at two time points. Parents and/or legal guardians completed the PSQ pre- and post-RME. Those with a positive PSQ and at high risk for OSA based on clinical history and symptoms were offered referrals to undergo a polysomnogram (PSG). Given that the PSQ is a comparable measure to PSG in those with a positive PSQ, we can only really measure a change in PSQ score for those who had a positive PSQ score pre-RME. Thus, our sample size is the number of subjects with a positive PSQ pre-RME. To obtain a power of 80% and a two-sided alpha of 0.05, sample size calculation yielded 17 subjects.

RME was achieved with a maxillary expander placed against the palate by cementation to molar bands. There is a screw at the midline that the caregiver turned 90 degrees once daily. Each 90 degree turn resulted in .25 mm of expansion. The goal is 9 mm of expansion, which can take 36 days, and the subject will return to the clinic in 2 week intervals. After desired expansion is achieved the expander is left in place at the last setting for the same number of days it took to expand 9 mm (approximately 2 months). A retainer was placed after the expansion for an additional 4 - 5 months, as per current practice. During the clinic visits after RME removal and placement of the retainer, post PSQ was given to parents and/or legal guardians. If a subject had a pre-RME PSG, then he/she would have a post-RME PSG as well.

Cone beam computed tomography (CBCT) data were utilized to evaluate airway at both pre- and post-RME time points, and the volumetric data gathered from airway analysis was related to the presence and severity of OSA as indicated by the PSQ score. As discussed in the introduction, PSQs are comprised of a one-page Sleep

Related Breathing Disorder (SRBD) scale with 22 closed response questions validated against polysomnography and adenotonsillectomy outcomes. This scale was developed for clinical research purposes at the University of Michigan (U of Michigan 2006), and has a sensitivity of 83% and a specificity of 87% for OSA prediction. Each of the 22 questions answered yes (Y/S) scored 1 point, no (N) scored 0 points, or don't know (DK/NLS) was scored as missing. The number of symptom-items endorsed positively is then divided by the number of item answered positively or negatively; the denominator therefore excludes items with missing responses and items answered don't know. The result is a number, a proportion that ranges from 0.0 to 1.0. Scores $> .33$ are considered positive and suggestive of high risk for a pediatric sleep-related breathing disorder. This threshold is based on a validity study that suggested optimal sensitivity and specificity at the 0.33 cut-off (Figure 1). All individuals who were determined to be at high risk for OSA pre-treatment were offered information on how to pursue a diagnostic polysomnogram. Unfortunately, due to cost, none of the subjects went through with the polysomnogram.

Child's Name: _____
 Person completing form: _____

Study ID #: _____
 Date: ____/____/____

Please answer these questions regarding the behavior of your child during sleep and wakefulness. The questions apply to how your child acts in general during the past month, not necessarily during the past few days since these may not have been typical if your child has not been well. You should circle the correct response or *print* your answers neatly in the space provided. A "Y" means "yes," "N" means "no," and "DK" means "don't know."

1. WHILE SLEEPING, DOES YOUR CHILD:				
Snore more than half the time?.....	Y	N	DK	A2
Always snore?	Y	N	DK	A3
Snore loudly?	Y	N	DK	A4
Have "heavy" or loud breathing?	Y	N	DK	A5
Have trouble breathing, or struggle to breathe?	Y	N	DK	A6
2. HAVE YOU EVER SEEN YOUR CHILD STOP BREATHING DURING THE NIGHT?	Y	N	DK	A7
3. DOES YOUR CHILD:				
Tend to breathe through the mouth during the day?.....	Y	N	DK	A24
Have a dry mouth on waking up in the morning?	Y	N	DK	A25
Occasionally wet the bed?	Y	N	DK	A32
4. DOES YOUR CHILD:				
Wake up feeling unrefreshed in the morning?	Y	N	DK	B1
Have a problem with sleepiness during the day?	Y	N	DK	B2
5. HAS A TEACHER OR OTHER SUPERVISOR COMMENTED THAT YOUR CHILD APPEARS SLEEPY DURING THE DAY?	Y	N	DK	B4
6. IS IT HARD TO WAKE YOUR CHILD UP IN THE MORNING?	Y	N	DK	B6
7. DOES YOUR CHILD WAKE UP WITH HEADACHES IN THE MORNING?.....	Y	N	DK	B7
8. DID YOUR CHILD STOP GROWING AT A NORMAL RATE AT ANY TIME SINCE BIRTH?	Y	N	DK	B9
9. IS YOUR CHILD OVERWEIGHT?	Y	N	DK	B22
0. THIS CHILD OFTEN:				
Does not seem to listen when spoken to directly.	Y	N	DK	C3
Has difficulty organizing tasks and activities.	Y	N	DK	C5
Is easily distracted by extraneous stimuli.	Y	N	DK	C8
Fidgets with hands or feet or squirms in seat.	Y	N	DK	C10
Is "on the go" or often acts as if "driven by a motor".	Y	N	DK	C14
Interrupts or intrudes on others (eg., butts into conversations or games).	Y	N	DK	C18

Thank you!

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Figure 1. One page validated pediatric sleep questionnaire (U of Michigan 2006) in English

The volumetric CBCT airway analysis was done on anonymized scans using 3dMDvultus software (Atlanta, U.S.A). The airway superior and inferior borders were defined using the Regional Edit tool. The superior border was defined as a line connecting Sella and Posterior Nasal Spine. The inferior border was defined as a line connecting the most anterior region of the airway formed by the thyroid cartilage to the transverse arytenoid muscle at the level where the esophagus splits from the airway. Measurements of the total hypo and oropharyngeal airway volume and minimum cross sectional area were then calculated and recorded for each 2-mm distance over the entire length of the airway (Figure 2).



Figure 2. Landmarks in 3dMDvultus software to generate volumetric data of the airway of a subject

Lateral cephalogram measurements and transverse data was also examined on Dolphin Imaging software (Chatsworth, CA) for correlation with PSQ scores. Sagittal and dental measurements on pre- and post-treatment lateral cephalograms were done to analyze maxillary retrusion, amount of maxillary protraction, and correlation with PSQ. Sagittal measurements of ANB, Wits, Co-A, and Co-Pg were analyzed. Dental measurements of U1-SN, LI-MP, and interincisal angle were analyzed (Figure 3). For the transverse analysis we utilized the University of Pennsylvania CBCT Transverse Analysis (reference). The mandibular reference points that correlate with the mandibular skeletal base are the bilateral “MGJ”: landmarks and the maxillary reference point that correlates well with the maxillary skeletal base is designated as the bilateral “Mx” landmarks. The Mx landmarks, also known as the Jugale point, is at the depth of the concavities of the lateral maxillary contours at the junction of the maxilla and zygomatic buttress. It is measured on the axial slice of the CBCT where the coronal cut intersects the Mx landmarks. The MGJ points are located at the most buccal point of the cortical plate opposite the mandibular first molars at the level of the center of resistance (approximately coincident with the furcation of the molars). It is measured from the coronal cut through the mandibular first molars at the level of the furcation. The difference between the maxillary measurement and the mandibular measurement should be at least 5 mm, if the difference is less than 5 mm maxillary skeletal constriction is diagnosed (Figure 4).

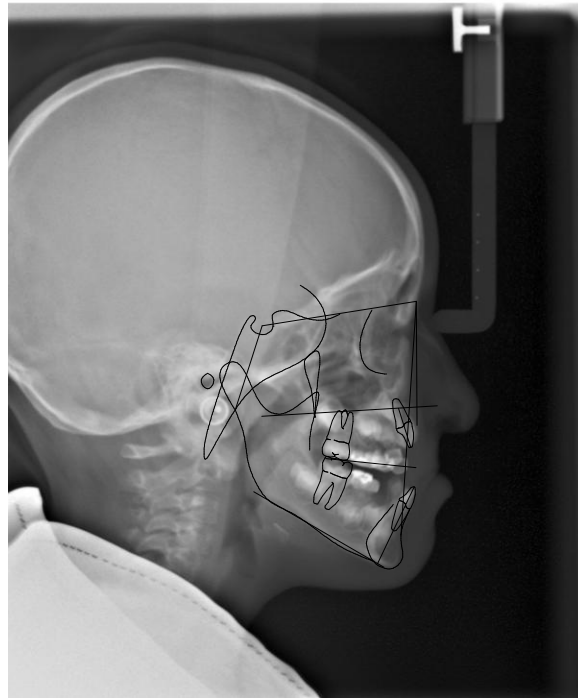


Figure 3. Lateral cephalometric tracing of a subject in the Dolphin Imaging Software

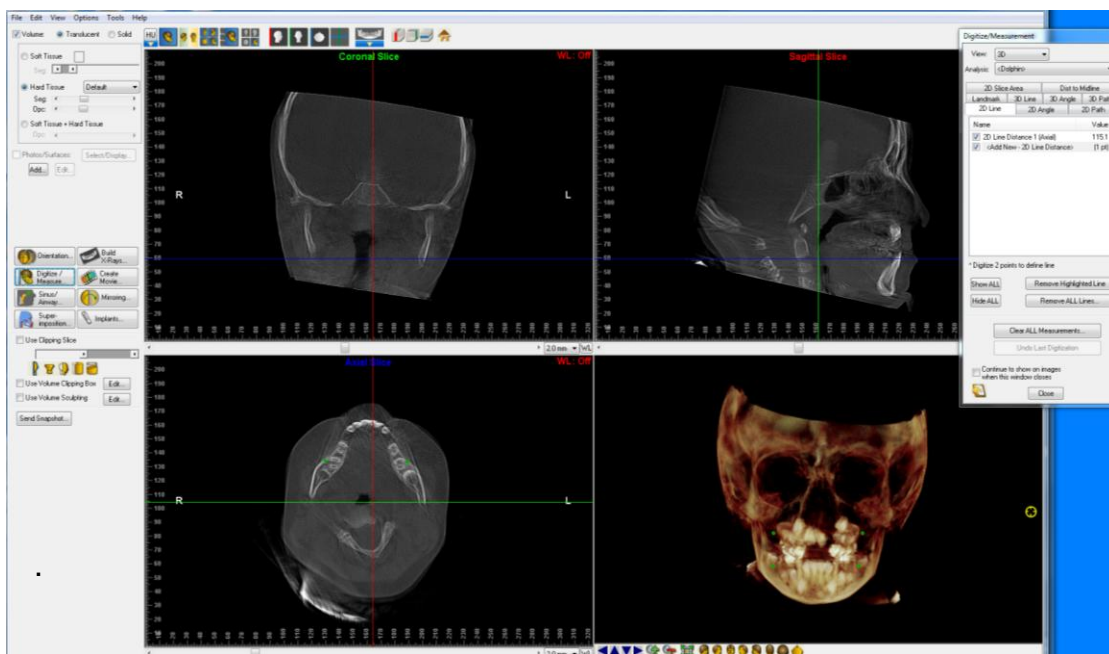


Figure 4. Landmarks in Dolphin Imaging software to measure the mandibular transverse dimension

Chapter 3. Results

Lateral cephalometric landmarks, transverse analysis, and airway volume and minimal cross sectional area measurements were tested for reliability using the Pearson Correlation Coefficient. Four randomly selected subjects were re-measured at two additional times, a minimum of four days apart, using each of the previously described methods. The intra-rater reliability testing showed a Pearson Correlation Coefficient ranging from .91 to .99, indicating good intra-rater reliability (Table 1).

<i>landmarks</i>	<i>confidence interval</i>	<i>range</i>	<i>p-value</i>
ANB	.99	(0.96, 0.999)	p<0.001
Wits	.99	(0.95, 0.999)	p<0.001
CoA	.91	0.66, 0.99	p<0.001
CoGn	.91	(0.68, 0.99)	p<0.001
U1SN1	.99	(0.98, 0.999)	p<0.001
LI-MP	.95	(0.80, 0.99)	p<0.001
Interincisal	.995	(0.98, 0.000)	p<0.001

Table 1. Intraclass correlation coefficients for lateral cephalometric data

Seven of the twenty-four recruited subjects scored positive on their pre-treatment Pediatric Sleep Questionnaire (PSQ). For those who tested positive prior to treatment, there was a significant decrease in their PSQ scores post-treatment. A Wilcoxon signed rank test showed a median (IQR) difference of -0.10 (-0.22, -0.07), with a p-value of 0.028, indicating a statistically significant difference (Figure 1).

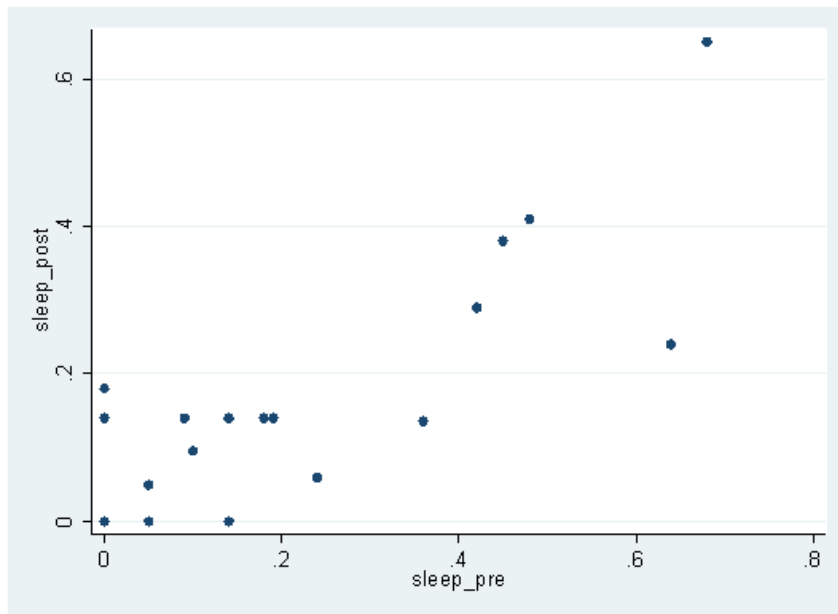


Figure 5. Scatter plot of Pediatric Sleep Questionnaire scores

Six of the seven subjects identified as a high risk for Obstructive Sleep Apnea (OSA) through their positive pre-treatment PSQ's filled out post-treatment PSQ's. One of the subjects dropped out of the study mid-treatment and we were unable to acquire post-treatment data for him. All six of the other subjects had a decrease in their PSQ scores post-treatment, and three of these six patients went from a high risk to a low risk for OSA post-treatment (Table 2).

<i>subject</i>	<i>pre-tx score</i>	<i>pre-tx risk</i>	<i>post-tx score</i>	<i>post-tx risk</i>
003/004	8/22 = .36	high	3/22 = .14	low
007/008	10/21 = .48	high	9/22 = .41	high
009/010	8/19 = .42	high	6/21 = .29	low
019/020	14/22 = .64	high	5/21 = .24	low
031/032	10/22 = .45	high	N/A	N/A
039/040	13/19 = .68	high	11/17 = .65	high
047/048	10/22 = .45	high	8/21 = .38	high

Table 2. PSQ scores of subjects at high risk for OSA pre-treatment

Given the high sensitivity (83%) and specificity (87%) of these PSQ'S for OSA prediction, they were used to determine whether other measurements that are commonly analyzed by orthodontists (like lateral cephalograms and transverse analysis), or measurements that could be easily and quickly done by providers with CBCT imaging in their office (airway volume and minimal cross sectional area), were correlated with the PSQs. Using Spearman Correlation Coefficient, no correlation was found between the pre-treatment sleep questionnaires and pre-treatment Minimum Cross Sectional Airway (Rho = - 0.37, p-value = 0.085), or the post-treatment sleep treatment sleep questionnaires and post-treatment Minimum Cross Sectional Airway (Rho= - 0.11, p-value 0.80). There was no correlation between any of the lateral cephalogram measurements and pediatric sleep questionnaire scores (Table 3), and no correlation between the transverse measurements and pediatric sleep questionnaire scores (Table 4).

Correlations between sleep questionnaire and lateral ceph measurements						
Lateral ceph measurement	sleep_pre			sleep_post		
	n	rho*	p-value	n	rho*	p-value
anb_pre	24	-0.20	0.35			
wits_pre	24	-0.18	0.40			
coa_pre	24	-0.01	0.95			
cogn_pre	24	0.15	0.47			
ulsn_pre	24	0.07	0.76			
limp_pre	24	-0.001	0.995			
intinc_pre	24	-0.007	0.97			
anb_post				8	0.01	0.98
wits_post				8	0.05	0.91
coa_post				8	0.32	0.44
cogn_post				8	-0.175	0.68
ulsn_post				8	0.098	0.82
limp_post				8	-0.24	0.56
intinc_post				8	0.02	0.95

* Spearman's rho correlation coefficient

Table 3. Spearman correlation between PSQs and lateral cephalogram measurements

Correlations between sleep questionnaire and transverse measurements						
Transverse measurement	sleep_pre			sleep_post		
	n	rho*	p-value	n	rho*	p-value
Mx_pre	22	-0.16	0.47			
Md_pre	22	0.29	0.19			
Mx_post				7	-0.15	0.75
MD_post				7	0.00	1.00

* Spearman's rho correlation coefficient

Table 4. Spearman correlation between PSQs and transverse measurements

While three of the twenty-four subjects dropped out of the study and were subsequently unable to fill out a post-treatment PSQs, seventeen of the subjects did not have post-treatment CBCTs and sixteen did not have post-treatment lateral cephalograms taken yet. Given the incomplete data set for final records, we were unable to thoroughly analyze the correlation between post-treatment pediatric sleep questionnaires and post-treatment measurements generated from final CBCTs and lateral cephalograms. These subjects are still undergoing treatment and their data will be available for analysis at a later date.

Chapter 4. Discussion

The first aim of our study was to identify the prevalence of sleep disordered breathing in the pediatric cleft population we routinely prescribe RME and maxillary protraction for using validated pediatric sleep questionnaires. We found a prevalence close to 30% in our recruited subject pool, which is on the higher end of the literature's currently estimated prevalence of 20 – 30%.¹⁻³

The second aim was to evaluate the effect of the expansion and protraction treatment on the PSQ scores. As discussed in the introduction, there is evidence that RME improves symptoms of sleep disordered breathing in the general pediatric population with OSA³², but little research has been done in the pediatric cleft lip and/or palate population who have a more complicated and multifactorial etiology of upper airway obstruction. Our study suggests the standard phase I treatment for children with cleft lip and/or palate with RME and maxillary protraction through facemask or forward-pull headgear therapy also improves symptoms of sleep disordered breathing. The exact mechanism for this improvement is not fully comprehended, reducing nasal airway resistance, raised tongue posture and relatively enlargement of pharyngeal airway may be contributing factors. Further research needs to be done to fully appreciate these effects.

The third aim of our study was to determine if volumetric and MCA data from the CBCT, the lateral cephalogram measurements, and the transverse analysis measurements correlated with the PSQ scores. Orthodontists routinely consider lateral cephalogram and transverse measurements when diagnosing and treatment planning, and many practitioners with CBCT machines in their offices extrapolate relevant

information from the airway measurements generated from 3-dimensional imaging. None of these measurements had a significant correlation with the validated pediatric sleep questionnaire scores. While nasal airway has been shown to be restricted in patients with cleft palate due to maxillary constriction¹⁹, recent studies analyzing CBCT airway volume has not shown the total pharyngeal airway volume or the MCA to be compromised in these patients²⁷. The popularity of 3-dimensional imaging in the orthodontic field has been growing along with interest in how routine treatment might affect the airway. It is well known that airway cannot be evaluated in 2-dimensional lateral cephalograms, but it is tempting for many providers to try and utilize airway volume measurements generated from CBCT data to inform diagnosis and treatment decisions. Previous research has supported the concept that minimum cross sectional area below a certain threshold has a high probability of OSA prediction³³, but our results did not show a correlation between PSQs and MCA. Specifically, the probability of severe OSA has been shown to be high with a MCA below 52 mm squared, an intermediate probability of OSA if the MCA is between 52 and 110 mm squared, and a low probability if the MCA is greater than 110 mm squared³³. It is possible that the differences in airway volume increase between patients associated with growth at this age prevented the same trend to be seen in these subjects. Previous literature has shown that the smallest cross sectional area of the airway occurred in younger subjects and reliably increased with age in both genders, with the rate of growth increasing faster in males than females after 11 years of age³⁴. It was shown that there is no difference between the genders airway volume or minimum cross sectional airway in the age range 7 to 11 years old, but that the airway was significantly smaller in those patients

identified clinically as mouth breathers as compared to nasal breathers³⁴. Evidence for 3-dimensional imaging to evaluate airway is still controversial at this time. We do not yet have reliable methods for evaluating the snapshot the CBCT provides of the dynamic nature of the airway.

The authors would have expected that there would have been a correlation found between maxillary constriction in the transverse analysis and positive pre-treatment PSQs. As discussed, previous literature suggests maxillary constriction is associated with features typically associated with OSA, like increase nasal resistance and subsequent mouth breathing. Maxillary constriction can also lead to alterations in tongue position that can result in retroglossal airway narrowing¹⁹. Furthermore, it surprised the authors that none of the lateral cephalogram measurements had a correlation with the pre-treatment PSQs. We had thought measurements reflecting the amount of maxillary retrusion would have correlated with positive PSQs, and other studies have shown OSA patients have a decreased facial A-P distance at cranial base, maxilla, and mandible levels as compared to normal controls that were BMI matched³⁵. Maxillary protraction has been shown to increase both post-palatal and nasopharyngeal airway in growing patients with skeletal Class III due to maxillary deficiency³⁶. It is possible that the sample size was not large enough to show a significant trend in this direction, or that the multifactorial etiology of upper airway constriction in the cleft palate population obscured the same trend in this study. It is also worth considering that most of the previous literature is looking at adults without craniofacial complications. In the pediatric, cleft palate population sleep questionnaires appear to be a more accurate

way to judge potential issues patients may have with sleep disordered breathing when they present in orthodontic clinics.

The major limitations of our study were the small number of subjects, incomplete post-treatment data, and lack of polysomnogram data. The significance of this study would be improved if an additional thirty patients were recruited, since our power analysis suggests seventeen subjects would need to test positive on their pre-treatment sleep questionnaires for the significance of our results to be optimal. Complete post-treatment data would be needed to draw conclusions regarding correlations between other measurements and post-treatment sleep questionnaires. Although validated pediatric sleep questionnaires have high sensitivity and specificity, polysomnograms are still the gold standard for diagnosing Obstructive Sleep Apnea and other sleep disordered breathing, so polysomnogram data would strengthen our study.

In conclusion, we found a prevalence of almost 30% of pediatric subjects with cleft palate with/without cleft lip at a high risk for Obstructive Sleep Apnea. Routine RME and maxillary protraction treatment appears to improve symptoms of sleep disordered breathing in young subjects with cleft palate with/without cleft lip. Other than pediatric sleep questionnaires, the measurements from the 3-dimensional imaging and lateral cephalograms we routinely use in the orthodontic clinic do not appear to correlate with the pediatric sleep questionnaires and the patient's risk for obstructive sleep apnea. Given the ease of use and limited time to administer a pre-treatment PSQ, it seems to be a valuable tool in clinical orthodontics. Our study suggests that when screening for OSA in the pediatric population, PSQs offer more reliable and accurate information regarding risk for sleep disordered breathing.

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