Assessment of Response to Rapid Maxillary Expansion in Pediatric Sleep-Disordered Breathing

BY

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THESIS
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This thesis is dedicated to my father, Mark Francis Joseph Equinda, whom I strive to make proud each and every day and whose love and support I feel so strongly even though he is longer here.
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<th>Description</th>
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<tr>
<td>AHI</td>
<td>Apnea-hypopnea index</td>
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<tr>
<td>A/N</td>
<td>Adenoid/nasopharyngeal</td>
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<td>BMI</td>
<td>Body mass index</td>
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<tr>
<td>CBCT</td>
<td>Cone-beam computed tomography</td>
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<tr>
<td>CT</td>
<td>Computed tomography</td>
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<tr>
<td>ENT</td>
<td>Otorhinolaryngology</td>
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<td>OAI</td>
<td>Obstructive apnea index</td>
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<td>OSA</td>
<td>Obstructive sleep apnea</td>
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<td>PAS</td>
<td>Posterior/pharyngeal airway space</td>
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<td>PSG</td>
<td>Polysomnography</td>
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<td>PSQ</td>
<td>Pediatric Sleep Questionnaire</td>
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<td>RME</td>
<td>Rapid maxillary expansion</td>
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<td>RPA</td>
<td>Retropalatal airway space</td>
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<td>SBD</td>
<td>Sleep-disordered breathing</td>
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<td>SRBD</td>
<td>Sleep-related breathing disorders</td>
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<td>T&amp;A</td>
<td>Tonsillectomy and adenoidectomy</td>
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SUMMARY

This retrospective cohort study was conducted to investigate the difference in study variables between surgical and non-surgical pediatric subjects with sleep-related breathing disorders (SRBD) after treatment with rapid maxillary expansion (RME). Subjects were referred to an orthodontist in private practice in Seoul, South Korea by otorhinolaryngology (ENT) physicians due to airway or sleep-related symptoms and were consecutively treated with RME. At baseline, lateral cephalograms were taken and Pediatric Sleep Questionnaires (PSQ) were administered to the subjects’ caregivers. PSQ were again administered to caregivers anywhere from two months to three years after removal of the RME appliance as a measure of the subjects’ response to treatment. Study variables included age of subject at the start of RME (years), gender, body mass index (BMI) (kg/m^2), total amount of expansion (mm), pre-RME PSQ score, post-RME PSQ score, and 12 lateral cephalometric variables.

Fifty-eight (58) subjects met the inclusion criteria. The surgical group consisted of 15 subjects who had tonsillectomy and adenoidectomy (T&A) performed prior to RME and lateral cephalogram capture. The non-surgical group consisted of 43 subjects who did not have T&A performed. The subjects were classified into subgroups defined as positive responders and non-responders based on pre- and post-RME PSQ scores as well as the percentage change in the score from baseline.
SUMMARY (continued)

The findings in this study on a population with symptoms of SRBD showed that in positive responders, those who had undergone T&A had higher mean ANB angles, lower mean PAS measurements, and higher mean Linder-Aronson PNS-ad₂ measurements than those who did not undergo T&A. For high-risk positive responders, those who had undergone T&A had lower mean facial axis angles and PAS measurements than those who did not undergo T&A. Therefore, baseline cephalometric variables may be considered as a screening tool in determining response to RME.
1. INTRODUCTION

1.1 Background

The term, sleep-related breathing disorders (SRBD), encompasses multiple conditions associated with increased upper airway resistance during sleep. Obstructive sleep apnea (OSA) is perhaps the most severe of the SRBD due to its characterization by changes in blood oxygen and carbon dioxide levels and possible arousals (Smith et al. 2017). OSA affects 1-5% of school-aged children equally distributed between males and females, though the true prevalence is unknown (Masoud, Jackson, and Carley 2017; Holmes et al. 2017). The peak onset of SRBD symptoms in the pediatric population occurs between two and eight years of age (Quo, Hyunh, and Guilleminault 2017). OSA can be associated with symptoms including excessive daytime sleepiness, nocturnal enuresis, behavioral problems, learning disabilities, irritability, snoring and reported cessation of breathing or gasping for air during sleep (Masoud, Jackson, and Carley 2017). More serious sequelae of untreated or severe pediatric OSA can include right-sided heart failure, growth retardation, failure to thrive, and other cardiovascular complications (Chervin et al. 2000; Smith et al. 2017; Flores-Mir et al. 2013).

OSA diagnosis in children is derived from results of polysomnography (PSG) in conjunction with evaluation of conditions of daily living (Sato et al. 2012). Most children who have obstructive SRBD remain undiagnosed and therefore, early detection and treatment are crucial in mitigating the associated long-term health risks (Downey, Perkin, and MacQuarrie 1993; Huynh, Desplats, and Almeida 2016;
Specifically, a recent study concluded that the potential cognitive delays associated with SRBD are a result of the behavioral problems that are prevalent in the affected population. Early identification of these deficits may allow for timely attention to the underlying anatomical deviations (Smith et al. 2017).

Risk factors for pediatric OSA include adenotonsillar hypertrophy, obesity, asthma, exposure to tobacco smoke, low socioeconomic status, neuromuscular conditions, craniofacial anomalies, macroglossia, and mandibular or midface hypoplasia (Flores-Mir et al. 2013). Adenotonsillar enlargement is arguably the most common cause of snoring and OSA in the pediatric population and also causes impaired nasal airflow and nasopharyngeal obstruction (Abreu et al. 2008; Löfstrand-Tideström et al. 1999; Sato et al. 2012). The estimated frequency of adenoid hypertrophy is 19-58% among children six months through 15 years (Aydin et al. 2008). Behlfelt et al. reported differences in dental and craniofacial morphologies between children with and without enlarged tonsils. Those with enlarged tonsils showed “extended head posture, lower hyoid position, an antero-inferior posture of the tongue, more retrognathic and posteriorly inclined mandibles, larger anterior total and lower facial heights, larger mandibular plane angles, retroclined lower incisors, protruded upper incisors, shorter lower dental arches, less overbite, more overjet, and more common lateral crossbites” (Behlfelt 1990; Behlfelt, Linder-Aronson, and Neander 1990; Behlfelt et al. 1990). In children experiencing growth, alterations in morphology and head posture as a result of distressed breathing are partially reversible once any airway obstruction has been
removed (Solow et al. 1993). A systematic review and meta-analysis by Flores-Mir et al. in 2013 showed significant differences in SN-MP (increased), SNB (decreased), and ANB (increased) values in children with OSA when compared to controls, suggesting more vertical growth and Class II skeletal malocclusions in children with OSA (Flores-Mir et al. 2013).

Polysomnography (PSG) is considered to be the gold standard for diagnosis of SRBD, as it provides variables to quantify respiratory functions including oxygen saturation (SpO₂) and apnea-hypopnea index (AHI) (Fastuca et al. 2015). Unfortunately, this assessment is time-consuming, invasive, costly, technically complex and potentially not easily accessible for all patients (Chervin et al. 2000; Masoud, Jackson, and Carley 2017). The Pediatric Sleep Questionnaire (PSQ) is valid and reliable in identifying SRBD and is more feasible in a clinical setting for orthodontists or when PSG is unavailable (Chervin et al. 2000).

Several tools have been used for diagnosis of an obstructed posterior airway, including nasal resistance and airflow tests, nasoendoscopy, two-dimensional (2D) lateral cephalometry, and three-dimensional (3D) imaging, though no consensus has been reached on the gold standard procedure for making a reliable diagnosis. According to Major et al., the lateral cephalogram is likely the most frequently utilized tools of those listed above, particularly by dentists, due to its simplicity, cost-effectiveness, availability and reproducibility (Major, Flores-Mir, and Major 2006). Both 2D and 3D imaging provide limited information relevant to OSA and
according to a systematic review by Major et al. in 2014, lateral cephalograms used in conjunction with a thorough medical history is the best available approach for screening of adenoid hypertrophy by dentists (Major et al. 2014). Despite the increasing use of 3D imaging, 2D lateral cephalometric radiographs are more routinely taken in orthodontic practices and the upper airway can be objectively evaluated from these 2D images, though limited norms are available (Masoud, Jackson, and Carley 2017).

The literature describes OSA treatment including both medical therapies (e.g. continuous positive airway pressure devices, oral appliances, nasal devices, myofunctional therapy) and surgeries (e.g. soft tissue surgeries, maxillomandibular advancements, tonsillectomies, hypoglossal nerve stimulation, and tracheostomies) (Camacho et al. 2017). Additionally, rapid maxillary expansion (RME) has been used to treat patients with high-arched and/or narrow hard palates (transverse maxillary deficiency), who are predisposed to OSA and often have dental crowding and malocclusion (Camacho et al. 2017). RME is frequently used in orthodontic treatment to manage both skeletal and dental transverse maxillary discrepancies. Due to the anatomical relationship of the hard palate and the nasal cavity, RME has been prescribed for improving nasal airflow. Following expansion, studies have shown a significant decrease in nasal airway resistance and increase in nasal-cross sectional areas, resulting in improvement of nasal breathing (Fastuca et al. 2015).
This retrospective cohort study was conducted to investigate the effects of RME utilizing the PSQ as a subjective measure of SRBD symptoms. Additionally, this project will assess differences in study variables between surgical and non-surgical pediatric subjects with SRBD after treatment with RME. Specifically, cephalometric variables, measured on 2D radiographs routinely taken in orthodontic practices, will be explored as a possible screening tool in determining response to RME.

1.2 **Specific Aims**

The focus of this study was on subjects referred to the orthodontist by otorhinolaryngology (ENT) physicians due to persistent airway and sleep-related symptoms indicative of pediatric SRBD. The goal of this study was to investigate the difference in study variables between surgical and non-surgical pediatric subjects with SRBD after RME treatment. Additionally, this study explored the relationship between cephalometric variables and response to RME as measured by change in PSQ scores.

According to Chervin et al., total PSQ-SRBD scores ≥ 0.33 are considered positive and suggestive of high risk for pediatric SRBD (Chervin et al. 2000, 2007). For the purposes of this study, subjects who were at high risk for pediatric SRBD were defined as those with pre-RME total PSQ-SRBD scores ≥ 0.33.

In 2015, Chervin et al. defined symptomatic resolution of childhood obstructive sleep apnea syndrome (OSAS) by “a total PSQ-SRBD score ≥ 0.33 at
baseline, < 0.33 at 7-month follow-up, and at least 25% below baseline at follow-up” (Chervin et al. 2015). Based on these criteria, the following definitions should be noted for the purposes of this study:

“Surgical” subjects were defined as those who underwent T&A procedures and were referred to the orthodontist due to residual symptoms of SRBD. The T&A was performed prior to the baseline lateral cephalometric radiograph as well as the initiation of RME. “Non-surgical” subjects were defined as those who did not undergo T&A.

In all subjects, “positive responders” were defined as those who had post-RME total PSQ-SRBD scores that decreased by at least 25% below baseline. “Non responders” were defined as subjects who had post-RME total PSQ-SRBD scores that stayed the same, increased or decreased by less than 25% below baseline.

In subjects at high risk for pediatric SRBD with pre-RME total PSQ-SRBD scores ≥ 0.33, “positive responders” were defined as subjects who had post-RME total PSQ-SRBD scores that decreased to < 0.33 and by at least 25% below baseline. "Non responders" were defined as subjects who had post-RME total PSQ-SRBD scores that did not decrease to < 0.33 and/or stayed the same, increased, or decreased by less than 25% below baseline.
1.3 **Null Hypotheses**

1. There is no mean difference in study variables between surgical and non-surgical subjects when grouped by PSQ response and SRBD risk.

2. There is no relationship between cephalometric variables and response to RME as measured by change in PSQ scores in study subjects.
2. REVIEW OF LITERATURE

2.1 Sleep-Related Breathing Disorders

SRBD is considered an umbrella term for disorders involving abnormalities of respiration during sleep including, but not limited to, upper airway resistance, OSA, obstructive hypoventilation, and primary snoring (Holmes et al. 2017). According to the American Academy of Sleep Medicine Style Guide for Sleep Medicine Terminology, sleep-disordered breathing (SDB) is a broad term encompassing SRBD, such as OSA, and other abnormalities of respiration during sleep that do not meet the diagnostic criteria for a disorder, such as snoring (American Academy of Sleep Medicine 2016). In the United States, SDB affects approximately 10-20% of the population, many of which remain undiagnosed. Disturbed sleep patterns are related to increased risk for hypertension, myocardial infarction, stroke, diabetes, sleepiness-related accidents, cognitive impairments, and dementia, among others. Side effects in children include behavioral and cognitive deficits, failure to thrive, and increased utilization of health care services (Masoud, Jackson, and Carley 2017).

The most common type of SRBD is OSA, which is characterized by an absence of oral and nasal airflow despite persistent inspiratory efforts. The estimated prevalence of OSA in the American adult population is 17%, with men more commonly affected than women (Masoud, Jackson, and Carley 2017; Finkel et al. 2009). It has been estimated that more than 80-90% of adults with OSAS remain undiagnosed (Finkel et al. 2009; Chervin et al. 2000). Pediatric OSA affects
approximately 1%-5% of children and is equally distributed between males and females (Masoud, Jackson, and Carley 2017). The true prevalence of undiagnosed pediatric OSA remains unknown, though it is thought to be even higher than that in the adult population (Holmes et al. 2017; Chervin et al. 2000; Ishman et al. 2015). Collapsed upper airway pharyngeal muscles during sleep cause an airway obstruction that leads to a pause in breathing (Masoud, Jackson, and Carley 2017; Quo, Hyunh, and Guilleminault 2017). An intrinsic collapsibility of the pharyngeal muscles exists during sleep, as the tone and reflex responses are modified. Extrinsic factors affecting upper airway space, most notably the nasal cavity, and the retropalatal and retroglossal upper airway spaces, are known to increase the collapsibility of the upper airway. When respiratory functions are modified due to an obstruction in children, the entire maxillomandibular complex can be affected in all dimensions, subsequently impacting the nasal cavity and retropalatal and retroglossal upper airway space (Quo, Hyunh, and Guilleminault 2017).

Studies have described associations between OSA and craniofacial morphologic changes including narrowed maxillae and dental arches, altered tongue position, clockwise rotation of the mandible, and narrowed width of the mandible (Quo, Hyunh, and Guilleminault 2017). When craniofacial and dental arch morphology was studied in four year old children with breathing obstructions as compared to an age-matched control group with ideal occlusion, children with obstructions were shown to have lower ratios of posterior to anterior total facial height as well as decreased cranial base angles. Minor insignificant differences were
found for SN to MP and ANS-PNS to MP. Compared with asymptomatic children, the obstructed children had narrower maxillae, deeper palatal heights, shorter lower dental arches, and higher prevalence of a lateral crossbite (Löfstrand-Tideström et al. 1999).

2.2 **Diagnosis of Sleep–Related Breathing Disorders**

2.2.1 **Polysomnography**

PSG is considered to be the gold standard in diagnosis of SRBD. PSG generates several records of activity during sleep, the most important of which is the apnea-hypopnea index (AHI). An apnea is a “cessation of nasal and oral airflow scored in children when there is at least 90% reduction in airflow compared to the pre-event baseline for at least two breaths”. An apnea is further characterized by respiratory effort during the period of absent airflow. During a hypopnea event, airflow is present, but reduced, and is defined by at least a 30% drop from a pre-event baseline for at least two breaths. A hypopnea is associated with at least 3% oxygen desaturation from pre-event baseline or an arousal. In children, AHI less than one indicates normal, AHI 1-4 indicates mild OSA, AHI 5-10 indicates moderate OSA, and AHI greater than 10 indicates severe OSA (Berry et al. 2012; Masoud, Jackson, and Carley 2017).

2.2.2 **Pediatric Sleep Questionnaire**

The Pediatric Sleep Questionnaire (PSQ) was developed and validated by Chervin et al. in 2000 as a method of assessing the presence of childhood SRBD and
prominent symptom complexes. Item reduction based on data from a randomly selected 50% of the subjects aged two -18 years produced a 22-item total SRBD score assessing snoring frequency, apneas, and difficulty breathing during sleep, among others, which was strongly associated with diagnosis of SRBD (p<0.0001). Diagnosis was also strongly associated with the following three subscores: “snoring (four items, p<0.0001), sleepiness (four items, p<0.0003), and behavior (six items, p<0.0001)” (Chervin et al. 2000). In two randomly divided groups, the selected criterion SRDB score led to sensitivities of 0.85 and 0.81 and specificities of 0.87 and 0.87. “The scales for childhood SRBD, snoring, sleepiness, and behavior are valid and reliable instruments that can be used to identify SRBD or associated symptom-constructs in clinical research when PSG is not feasible” (Chervin et al. 2000). A total PSQ-SRBD cutoff score of ≥ 0.33 has been shown to be effective in identifying patient’s who are at high risk for pediatric SRBD and warrant appropriate referrals (Chervin et al. 2007).

2.3 Treatment of Pediatric Sleep-Related Breathing Disorders

2.3.1 Tonsillectomy and Adenoidectomy

The upper airway of the respiratory tract extends from the nares and mouth to the pharynx, including the larynx. The pharynx is separated into three segments, the nasopharynx, oropharynx and hypopharynx. The most superior nasopharynx is found superior to the soft palate and posterior to the nasal cavity. The pharyngeal tonsils are found within the posterior wall of the nasopharynx. The middle segment, the oropharynx, is bordered by the soft palate superiorly and the epiglottis
inferiorly. The third segment, the hypopharynx, extends from the upper border of the epiglottis to the lower margin of the cricoid cartilage. Adenoids and tonsils reach their maximum size at approximately five years of age, after which they begin to shrink. While Scammon’s curve shows lymphoid tissues beginning to decrease in size around age 12, this assessment did not include tonsils and adenoids in the category of lymphoid tissue (Masoud, Jackson, and Carley 2017).

T&A has been employed as the first-line treatment for OSA in non-syndromic children since the 1970s (Pirelli, Saponara, and Guilleminault 2015). The two most common indications for T&A are recurrent throat infections and SRBD (Ingram and Friedman 2015). The Childhood Adenotonsillectomy Trial (CHAT), a randomized clinical trial including five to nine year old children with OSA, showed significant benefit for T&A compared to watchful waiting based on PSG and subjective symptom-related parent-reported scales (Marcus et al. 2013). The early T&A group had “significantly greater improvements in behavior, quality of life, and PSG outcomes and significantly greater reduction in symptoms” (Marcus et al. 2013). 79% of the treatment group experienced normalization of PSG findings as defined by a “reduction in both the AHI score to fewer than two events per hour and the obstructive apnea index (OAI) score to fewer than one event per hour” compared to 46% in the watchful waiting group (Marcus et al. 2013). While the difference in PSG normalization prevalence between the two groups was statistically significant, almost half of the watchful waiting group normalized, which indicated that a period of observation may be a valid therapeutic option (Marcus et al. 2013).
A recent study by Isaiah et al. assessed OSA resolution and persistence in 74 children aged two-12 years old who underwent T&A due to diagnoses of severe OSA as defined by an AHI > 30. Following T&A, 32% of subjects displayed complete resolution of OSA (AHI < one) and 80% experienced a decrease in AHI to less than five. While significant improvements of OSA were appreciated following T&A, complete resolution was only achieved in approximately one-third of the subjects. Hypercapnia and hypoxemia levels at baseline were found to be the best predictors of OSA persistence following T&A (Isaiah et al. 2017).

Interestingly, studies have shown that after both short- and long-term follow-up, residual symptoms and elevated AHI have presented after T&A (Pirelli, Saponara, and Guillemainault 2015). A prospective study by Lesinskas and Drigotas in 2009 showed that 82.7% of subjects’ parents reported improved quality of life and decreased symptoms 12-24 months following adenoidectomy. Adenoid regrowth was identified via transnasal fibroscopy in 19.1% of patients, though clinical manifestations were not present. The study also identified that adenoid regrowth occurred more commonly in children younger than five years of age or in those who were treated with antibiotics postoperatively on numerous occasions (Lesinskas and Drigotas 2009).

Recently, partial tonsillectomy, also referred to as tonsillotomy or intracapsular tonsillectomy, with or without adenoidectomy, has been applied to the
treatment of sleep apnea and upper airway obstruction. A recent retrospective study evaluated children with OSA under the age of 12 years old at one year following either total T&A (TA) or partial intracapsular tonsillectomy and adenoidectomy (ITA), with over 1,000 subjects included in each treatment group. At one-year follow-up, 7.3% of children in the TA group exhibited adenoid regrowth determined by a subjective grading scale and only 1.4% displayed symptoms. In the ITA group, 4.7% had adenoid regrowth, which is significantly different from that of the TA group (Babademez et al. 2017).

2.3.2 Rapid Maxillary Expansion

RME was first described as a potential treatment modality for adult OSA by Cistulli, Palmisano, and Poole in 1998 based on documented efficacy of RME on other conditions including enuresis, diaphoresis, asthma, and allergies (Cistulli, Palmisano, and Poole 1998). Quo, Hyunh, and Guilleminault showed that the majority of children with SDB aged three to 14 years old had improved sleep scores and symptoms following bimaxillary expansion (Quo, Hyunh, and Guilleminault 2017). In 2004, Pirelli, Saponara, and Guilleminault performed RME on 31 children, mean age 8.7 years, with normal BMI, constricted maxillae, absence of adenoid hypertrophy, and a diagnosis of OSA based on PSG. The subjects had a mean baseline AHI of 12.2 events per hour, which dropped below one event per hour in all subjects at 4-month follow-up (Pirelli, Saponara, and Guilleminault 2004). A 12-year annual follow-up study on 23 of the subjects using PSG and computed tomography
(CT) imaging confirmed the stability of RME for treatment of pediatric OSA (Pirelli, Saponara, and Guilleminault 2015).

A most recent systematic review and meta-analysis by Camacho et al. looked at sleep study outcomes in children who had undergone RME as treatment for OSA. The review concluded that improvements in AHI and lowest oxygen saturation have consistently been seen in children undergoing RME, with the majority of literature reporting short-term data (≤ three years follow-up). At ≤ three years follow-up, AHI decreased by 70% and the cure rate, defined as AHI < one per hour, was 25.6%. Furthermore, subjects who had undergone T&A or had smaller tonsils showed greater improvement in AHI (73-95% reduction) compared to those with large tonsils (61% reduction). At > three years follow-up, AHI was reduced by 79% (Camacho et al., 2017).

In 2015, Fastuca et al. evaluated changes in airway volume and respiratory functions in patients undergoing RME. Cone beam computed tomography (CBCT) and PSG examinations before and after RME showed significant increases in upper, middle, and lower airway volumes, increased oxygen saturations, and improved AHI. Baseline middle and lower airway volume significantly negatively correlated with oxygen saturation increase after RME and therefore, improvement in respiratory performance is greater when baseline middle and lower airway volume are smaller (Fastuca et al. 2015).
A study by Vinha et al. looked at multislice CT scans of non-growing patients with either a unilateral or bilateral posterior crossbite before and after surgically-assisted rapid maxillary expansion. Results showed significant airway enlargement in the sagittal plane of the middle level (measured at the most anterior inferior portion of the right lateral edge of the cervical atlas) as well as in the sagittal plane, transverse plane and total area of the lower level (measured at the lowest point of the odontoid process of the cervical axis). Significant airway enlargement was not found at the upper level, as defined by PNS. The anteroposterior increased depths were likely due to advancement of the tongue into the oral cavity as a result of the maxillary expansion in the transverse dimension (Vinha et al. 2016).

In 2013, Chang et al. confirmed findings of previous studies and also found significant increase in the cross-sectional area of the upper airway at the level of PNS to basion following RME (Chang et al. 2013).

Lione et al. evaluated RME effects using low-dose CT before treatment, at the end of active expansion with the expander in place, and 6 months after the end of active expansion when the expander was removed. Anterior, middle, and posterior sutural widths as well as the pterygoid width measured at the lateral pterygoid plates all increased significantly following active expansion. Between the end of active expansion and the retention phase, the sutural width values decreased significantly and when comparing the pretreatment sutural widths to those at the retention time point, the values were not statistically significant. The pterygoid
width though, increased significantly from the pre-treatment to the retention time point (Lione et al. 2008).

In a case-control study, Seto et al. evaluated maxillary morphology in adults with OSA as well as controls. 50% of subjects with OSA compared to only 5% of controls had posterior transverse discrepancies. All subjects with OSA had significantly reduced inter-canine, inter-premolar, and inter-molar distances (narrower arch forms) as well as shorter maxillary depths. Subjects with OSA displayed significantly greater arch tapering and smaller maxillary to mandibular and maxillary to facial width ratios (Seto et al. 2001).

Some studies though, show that limits to RME do exist. In the study by Quo et al., one patient out of 16 in the severe OSA category with AHI > 10 experienced an increase in AHI after bimaxillary expansion. In the moderate group with AHI ≥ 5 and AHI ≤ 10, five out of 17 patients had an increase in AHI. In the mild group with AHI < 5, nine out of 12 patients had an increase in AHI (Quo, Hyunh, and Guilleminault 2017). In 2014, Villa et al. studied T&A, RME, and a combination of both as treatment options for OSA. PSG was performed before the treatment intervention/s and one year after. In the group of 25 children who underwent T&A, AHI decreased. In the group of 22 children who underwent RME, AHI increased in four patients (Villa et al. 2014).
2.4 **Airway Imaging in Orthodontic Practice**

2.4.1 **Lateral Cephalometrics**

The lateral cephalogram is a standardized radiograph taken in the sagittal plane commonly used by orthodontists. This imaging modality is simple, readily available, economical, and reproducible and has long been used in the assessment of upper airway obstruction (Lertsburapa, Schroeder, and Sullivan 2010; Major, Flores-Mir, and Major 2006). Despite the limitations of lateral cephalometry, which include anatomic discrepancies due to rotations and head positioning, respiratory cycle, and lack of patient cooperation, numerous studies have shown correlations between various cephalometric analyses and other methods of direct visualization of the airway (Lertsburapa, Schroeder, and Sullivan 2010).

A 2006 systematic review by Major et al. concluded that regarding the diagnosis of adenoid hypertrophy and posterior airway obstruction, the most useful role of lateral cephalometry is as a screening tool to determine if more rigorous ENT follow-up is warranted. The review also concluded that since no consensus has been reached on what the most useful landmarks are for quantification of adenoid and upper airway size, it is recommended that clinicians utilize a variety of measures in their analyses (Major, Flores-Mir, and Major 2006).

A follow-up systematic review by Major et al. in 2014 concluded that the most accurate approach to evaluating nasopharyngeal obstruction on a lateral cephalogram is by assessing the patent airway size instead of the adenoid size. It
confirmed that at the time of publication, no ideal tool existed for dentists when screening for adenoid hypertrophy due to constraints related to access to imaging, radiation dosages, and suboptimal diagnostic accuracy. Lateral cephalograms (good to fair sensitivity) and a thorough medical history (good specificity) have their limitations when used independently, but when used in combination serve at the best available tool to dentists for screening for adenoid hypertrophy (Major et al. 2014).

2.4.1.1 Cephalometric Variables

According to a systematic review by Major et al. in 2006, both quantitative and subjective adenoid grading on lateral cephalograms had reasonable correlations to true adenoid size and therefore, lateral cephalograms performed relatively well in evaluating adenoid size. Adenoid size had clinically useful correlations using area measurements, while linear measurements were essentially meaningless. As compared to adenoid size, the ability of lateral cephalograms to diagnose a small posterior nasopharynx was less conclusive. Only the McNamara line was consistently useful largely because of its dependency on adenoid size. The McNamara line was the only specific measurement evaluated in the systematic review with limited validation from multiple studies (Major, Flores-Mir, and Major 2006).

A more recent systematic review by Major et al. showed that lateral cephalograms had “good to fair sensitivity (61-75%) and poor specificity (41-55%)
for adenoid size assessment compared to excellent to good specificity for airway patency assessment (68-96%)” (Major et al. 2014). Basing diagnosis on the size of the airway tended to have better specificity: airway/nasopharynx (A/N) ratio had 95% specificity, airway-palate ratio had 96% specificity, minimum airway size (McNamara line) had 86% specificity. The most consistent technique for evaluating nasopharyngeal obstruction on a lateral cephalogram is by assessing airway size rather than adenoid size (Major et al. 2014).

The adenoid/nasopharyngeal (A/N) ratio was developed by Fujioka et al. in 1979 and was found to reliably characterize adenoid size and patency of the nasopharyngeal airway. 94% of patients with subjectively defined enlarged adenoids had an A/N ratio of greater than 0.80 (Fujioka, Young, and Girdany 1979). In 1992, Wormald and Prescott compared radiological assessment methods with clinical and endoscopic findings and found 41% sensitivity and 95% specificity using the A/N ratio (Wormald and Prescott 1992). Caylakli et al. in 2009 found that A/N ratio correctly measured the size of the adenoids in patients suspected to have adenoid hypertrophy when correlated to endoscopic exam (Caylakli et al. 2009). Lertsburapa et al. confirmed these findings in 2010 by determining that A/N ratio correlated well with findings of the intra-operative mirror exam (Lertsburapa, Schroeder, and Sullivan 2010).

Linder-Aronson and Henrikson in 1973 evaluated linear measurements A1 (pm-ad₁ in mm) and A2 (pm-ad₂ in mm) and area measurement A3 (pm-ad₁-ad₂-pm
in mm²). Linear measurements A1 and A2 were equally useful for measuring the anteroposterior nasopharyngeal airway and no additional information was gained by calculating the area measurement A3, deeming the variable unnecessary (Linder-Aronson and Henrikson 1973). Holmberg and Linder-Aronson in 1979 evaluated adenoid size on lateral skull radiographs subjectively on a five-index scale and quantitatively as a linear measurement from ad₁-ba in mm. Adenoid area was measured as a relationship between the area ad₁-ad₂-ho-ba-ad₁ and the area pm-ho-ba-pm as a percentage. Significant correlations were found between clinical evaluation of adenoid size via posterior rhinoscopy and radiographic subjective adenoid grade, size in mm, and area as a percent with coefficients of 0.71, 0.57, and 0.60, respectively. The relationship between airflow velocity and adenoid size was less strong, but still showed a highly significant negative correlation (Holmberg and Linder-Aronson 1979). Linder-Aronson and Leighton in 1983 also measured ad₁-pm and ad₂-pm in mm as indicators of sagittal depth of the airway through the nasopharynx (Linder-Aronson and Leighton 1983). According to the Rocky Mountain Orthodontics Data Services, the Linder-Aronson AD₁ and Linder-Aronson AD₂ variables are “used to determine the cause of airway obstruction and are measured as the distance from PNS to the nearest adenoid tissue in a line from PNS to Basion and the distance from PNS to the nearest adenoid tissue in a line from PNS perpendicular to Sella-Basion”, respectively (Rocky Mountain Orthodontics 2017).

Sato et al. assessed the value of craniofacial and pharyngeal airway morphology evaluation in the treatment of children with OSA. The non-op group
consisted of children with OSA who had undergone drug therapy alone (antibiotic or anti-allergy) and the op group consisted of those who had undergone both drug therapy and surgical therapy (T&A). Between groups, significant differences were found in the facial axis, mandibular plane angle (FH-MP), D-Ad$_1$ (“distance between PNS and the nearest adenoid tissue measured along PNS-Ba”), D-Ad$_2$ (“distance between PNS and the nearest adenoid tissue measured along a line from the PNS perpendicular to the S-Ba plane”) and upper pharynx (“shortest distance from the upper surface of the palatine velum to the adenoid tissue”), among others (Sato et al. 2012). Facial axis, D-AD$_1$, D-AD$_2$, and upper pharynx values were significantly lower and the mandibular plane angle was significantly higher in the op group (Sato et al. 2012).

Lee et al. in 2009 utilized both the retropalatal space as the “narrowest posterior airway space at the level of the soft palate” and the retrolingual space as the “narrowest posterior airway space at the level of the tongue base” as outcome measures of upper airway changes associated with a mandibular advancement device in patients with OSA. Both the retropalatal and retrolingual spaces increased with use of the mandibular advancement device (C. H. Lee et al. 2009). Posterior airway space (PAS) was evaluated by Lee et al. in 1997 “by a line drawn from Point B through Go, which intersects the base of the tongue and posterior pharyngeal wall” (J. J. Lee, Ramirez, and Will 1997).
Sriram and Andrade in 2014 investigated the effect of surgical jaw movements on the pharyngeal airway space, particularly the pharyngeal width, which was measured on lateral cephalogram as the “distance between the point on the posterior border of the dorsum of the tongue closest to the pharyngeal wall and the corresponding point on the posterior pharyngeal wall, parallel to the FH plane”. As expected, surgical movements do have an effect on the pharyngeal airway space. A significant positive correlation was found between the PAS width and mandibular distraction osteogenesis with and without genioplasty. PAS width was unchanged with advancement of the maxilla (Sriram and Andrade 2014).

In 2008, Muto, Yamazaki and Takeda utilized lateral cephalograms to investigate the PAS at the level of both the soft palate and base of the tongue in females with normal, retrognathic and prognathic mandibles as determined by SNB values. The PAS widths were largest in the prognathic group and smallest in the retrognathic group. When the relationship between the PAS and craniofacial morphology was evaluated, facial axis was shown to be positively correlated with both measures of PAS in the group of subjects as a whole (Muto, Yamazaki, and Takeda 2008).

In 2016, Koay et al. showed that Herbst appliance treatment in Class II adolescents increased the oropharyngeal and hypopharyngeal airway dimensions as measured on a lateral cephalogram. In addition, a negative correlation was found between the change in depth of the retroglossal pharynx (measured at the base of
the tongue) and the mandibular plane angle (SN-MP). In addition to SN-MP, skeletal morphology was represented by SNA, SNB and ANB (Koay et al. 2016).

Quo et al. in 2016 found SN-MP to be a predictor of response to bimaxillary expansion. Patients with a smaller SN-MP, or counterclockwise mandibular growth (retrognathia) showed worsening of SRBD symptoms with bimaxillary expansion while those with clockwise mandibular growth showed greater improvement in symptoms (Quo, Hyunh, and Guilleminault 2017).

Lofstrand-Tidestrom et al. in 1999 showed that children with obstruction had smaller cranial base angles as measured by SN-Ba and lower posterior to anterior total facial height ratios. Minor insignificant differences were seen for SN-MP and ANS/PNS-MP (Löfstrand-Tideström et al. 1999).

2.4.2 Three-Dimensional Imaging

While lateral cephalometric radiographs are valuable in airway assessment, limitations exist and include differential magnification and overlapping of structures. 3D CBCT delineates soft tissue structures from airway spaces and volumetric measurements correlate nearly 1:1 with the actual airway volume. Semi-automated software can even calculate desired measurements (Masoud, Jackson, and Carley 2017). While 3D imaging is invaluable for research in airway imaging, the cost associated with this modality may mean that it will never be economically feasible for everyday diagnostic use (Major, Flores-Mir, and Major 2006). Relative to
medical computed tomography (CT) and magnetic resonance imaging (MRI), CBCT does offer lower radiation and cost as well as easier access. Important factors to consider in the consistency of 3D upper airway analysis include image quality, segmentation accuracy, image threshold, selected anatomical boundaries, head posture, stage of respiration and swallowing, and tongue and mandibular position. These critical issues have also hindered the development of CBCT airway volume norms (Masoud, Jackson, and Carley 2017).
3. METHODOLOGY

3.1 IRB

A “Determination of Whether an Activity Represents Human Subjects Research” application was completed for this study’s protocol (# 2017-0111). The application was submitted to the University of Illinois at Chicago (UIC) Office for the Protection of Research Subjects (OPRS), Institutional Review Board (IRB), which determined that this study does not meet the definition of human subject research and therefore, the study could be conducted without further submission to the IRB (Appendix A).

3.2 Subjects

Sixty (60) pediatric subjects were referred to an orthodontist in private practice in Seoul, South Korea by ENT physicians due to airway or sleep-related symptoms and were consecutively treated with RME between 2009 and 2016. Two subjects were excluded from the study due to non-diagnostic cephalograms and therefore, 58 subjects met the inclusion criteria; 32 female and 26 male. The age at the start of RME ranged from 3.2 years to 14.0 years with a mean age of 8.0 years ± 2.49 years. The BMI ranged from 13.2 kg/m² to 24.6 kg/m² and the mean BMI was 16.5 kg/m² ± 2.45 kg/m². The total amount of maxillary expansion ranged from 3.5 mm to 10.5 mm and the mean amount of expansion was 7.48 mm ± 1.53 mm.

Subjects were divided into two groups: surgical - had T&A performed (n=15), and non-surgical - did not have T&A performed (n=43). The subjects were further
classified into the subgroups positive responders and non-responders based on PSQ scores and the percentage change in the scores from baseline.

Lateral cephalograms were taken at baseline. In order to measure subjects’ responses to treatment, PSQ were administered to caregivers at baseline and again anywhere from 0.2 years to 3.0 years after RME removal (mean = 0.6 years ± 0.54 years). In some cases, an additional phase of treatment following RME was indicated, which could include fixed appliances, headgear, and/or dental extractions. When additional treatment was rendered, the post-RME PSQ was given just prior to the initiation of the second phase of treatment.

The type of expansion appliance used for each subject was selected according to permanent maxillary molar and first premolar eruption. Before first molar eruption, a bonded RME was used. After first molar eruption, a hyrax RME with 2 bands was used. After first molar and first premolar eruption, a hyrax RME with 4 bands was used.

The RME activation protocol was two turns per day for one-three weeks. In the absence of a posterior crossbite and lingually tipped maxillary and mandibular molars, expansion took place twice per day for one week. In the presence of a posterior crossbite and/or lingually tipped maxillary and mandibular molars, expansion was prescribed twice per day for two weeks. Expansion lasting twice per day for three weeks was reserved for cases with severe posterior crossbites. During
expansion, patients were seen at one-week intervals to assess expansion progress and SRBD symptoms. Expansion was stopped once symptoms resolved and/or the patient was almost in buccal crossbite.

3.3 **Design**

This study was a retrospective cohort study. No controls were provided for this study by the private practice orthodontist responsible for the treatment of the subjects. A coded spreadsheet was provided with detailed descriptive variables for the 58 subjects and therefore, no protected health information was disclosed to the investigator. De-identified pre-RME lateral cephalograms, pre-RME PSQ, and post-RME PSQ were also provided.

3.3.1 **Selection Criteria**

**Inclusion criteria**

- Females and males aged 3-14 years at the start of RME
- Subjects referred to the orthodontist by ENT physicians due to airway and/or sleep-related symptoms
- Treatment with RME
- Diagnostic quality lateral cephalometric radiographs taken prior to RME
- PSQ completed both before initiation of RME and after completion of RME/prior to initiation of any further treatment
- Phase I orthodontic treatment only or prior to any phase II
orthodontic treatment

**Exclusion criteria**

- Distorted or blurred cephalometric radiographs
- Use of orthodontic appliances other than an RME or Schwartz expander
- Craniofacial anomalies
- Missing pre-RME cephalometric radiographs
- Missing pre-RME PSQ or post-RME PSQ

### 3.3.2 Study Variables

- Age at the start of RME (years)
- Gender
- BMI (kg/m\(^2\))
- Total amount of expansion (mm)
- History of T&A
- Pre-RME PSQ score
- Post-RME PSQ score
- Percentage change in PSQ score from baseline

12 lateral cephalometric variables (Figure 1):

- Cranial base (1)
  1. SN-Ba: Sella-Nasion to Basion (°)
- Vertical (2)
2. Facial axis: Nasion-Basion to Pt-Gnathion (°)

3. SN-MP: Sella-Nasion to Menton-Constructed Gonion (°)

- Anteroposterior (3)

4. SNA: Sella-Nasion to Nasion-Point A (°)

5. SNB: Sella-Nasion to Nasion-Point B (°)

6. ANB: Point A-Nasion to Nasion-Point B (°)

- Airway (6)

7. Adenoid tissue/nasopharyngeal aperture (A/N) ratio: Adenoid tissue (A) was defined as the “distance from the adenoid (point of maximum convexity along the inferior margin of the adenoid shadow) to the sphenobasocciput (anteroinferior edge of the sphenobasoccipital synchondrosis or the site where the posteroinferior margin of the lateral pterygoid plates crosses the floor of the bony nasopharynx)” in mm. The nasopharyngeal aperture (N) was defined as the “distance from the sphenobasocciput to the posterior superior edge of the hard palate (PNS)”. The A/N ratio was then calculated by dividing A by N (Fujioka, Young, and Girdany 1979).

8. Posterior airway space (PAS), also known as the retrolingual space, was defined as the “narrowest posterior airway space at the level of the tongue base” measured in mm (C. H. Lee et al. 2009). The PAS was evaluated by a line drawn from point B through Gonion (B-Go). The anterior point was selected where the line B-Go intersected the base of the tongue (posterior border of the dorsum of the tongue closest to the pharyngeal wall) and the posterior point was selected where the line B-Go intersected the posterior pharyngeal wall. The PAS was then
measured as the linear distance in mm from the base of the tongue to the posterior pharyngeal wall at the points of intersection with the line B-Go.

9. Retropalatal airway space (RPA) is the narrowest PAS at the level of the soft palate measured as the minimum linear distance between two points. The anterior point was selected at the soft palate and the posterior point was selected at either the posterior pharyngeal wall or the adenoid shadow dependent upon where the narrowest PAS was located.

10. McNamara line is the narrowest PAS at the level of the adenoid measured as the minimum linear distance between two points. The anterior point was selected at the dorsal aspect of the soft palate and the posterior point was selected at the adenoid shadow dependent upon where the narrowest PAS was located.

11. Linder-Aronson PNS-ad₁ is the sagittal depth of the nasopharyngeal airway measured as the linear distance from PNS to the point ad₁, in mm. Ad₁ was defined as the intersection of the line PNS to Basion with the posterior nasopharyngeal wall.

12. Linder-Aronson PNS-ad₂ is the sagittal depth of the nasopharyngeal airway measured as the linear distance from PNS to the point ad₂, in mm. Ad₂ was defined as the intersection of the line PNS to the midpoint of the distance from Sella to Basion (So) with the posterior pharyngeal wall.
Figure 1. Cephalometric landmarks and measurements
3.4 **Data Acquisition and Statistical Analysis**

De-identified lateral cephalograms were uploaded as jpeg files to Dolphin Imaging software (Version 11.9.07.24 Premium; Dolphin Imaging and Management Solutions, Chatsworth, California) and calibrated using the actual ear rod diameter of 16mm. When digitizing the radiographs, the diameter of the more magnified ear rod was measured by estimating a straight line passing through the center of the ring and selecting the two points at which the line intersected the ring's outer edge. This was chosen as the calibration method because rulers were not present on the majority of radiographs. Radiographs were digitally traced using a custom analysis created to measure the 12 cephalometric variables described in section 3.3.2. The principal investigator (MJE) was tested for intra-reliability by tracing ten cephalometric radiographs twice, one week apart. The ten selected radiographs were chosen at random by an online randomizer. The intra-class correlation coefficient was determined for each variable as an indicator of study method consistency for the variables measured. The correlation coefficient for all 12 variables was higher than 0.90 (p < 0.05), indicating a high degree of reliability.

Response to RME was measured by the total SRBD scale of the PSQ, which was administered to the caregivers of patients before and after treatment with RME. The SRBD scale utilizes 22 symptom items assessing snoring, apneas, and disordered breathing during sleep, among others. In this study, the 22-item PSQ was translated into a Korean version (Appendix B). Responses were quantified as “yes” = 1, “no” = 0, and “don't know” = discounted from the denominator of 22. The number
of “yes” was divided by the adjusted denominator in order to calculate the total PSQ-SRBD score. A score of $\geq 0.33$ ($\geq$ eight “yes”) suggests the diagnosis of SRBD and warrants referral to a sleep specialist (Chervin et al. 2000).

The percentage change of the total PSQ-SRBD score from baseline was calculated by subtracting the pre-RME total PSQ-SRBD score from the post-RME total PSQ-SRBD score. This difference was then divided by the pre-RME total PSQ-SRBD score (Chervin et al. 2015).

An analysis based on the descriptive statistics of a recently published article (Chervin et al., 2015), indicated that a sample size of approximately 10 subjects per group would be sufficient to achieve 80% power with 5% error type I to detect a mean PSQ score rate difference between two groups of subjects with symptoms of pediatric SRBD. The data analysis for the study variables used statistical tests for mean differences and associations. Statistical significance was set at $p < 0.05$. Data analysis was performed using IBM SPSS for Windows (Version 22.0, IBM Corp., Armonk, NY).
4. RESULTS

4.1 Results

Exploratory data analysis indicated that the majority of the cephalometric continuous variables had an approximately normal distribution. Study results were reported in terms of mean and standard deviation parameters, independent Student’s $t$-tests, and Pearson correlations. The groups discussed in the results are defined in section 1.2.

The 58 subjects included in this study were divided into two groups identified as positive responders ($n = 50$) and non-responders ($n = 8$). In all subjects, “positive responders” were defined as subjects who had post-RME total PSQ-SRBD scores that decreased by at least 25% below baseline. “Non-responders” were defined as subjects who had post-RME total PSQ-SRBD scores that stayed the same, increased or decreased by less than 25% below baseline. Within the group of 50 positive responders, 37 were non-surgical and 13 were surgical. “Surgical” subjects were defined as those who underwent T&A procedures and were referred to the orthodontist due to residual symptoms of SRBD. The T&A was performed prior to the baseline lateral cephalometric radiograph being taken as well as the initiation of RME. “Non-surgical” subjects were defined as those who did not undergo T&A.

Independent Student’s $t$-tests indicated statistically significant mean differences in the cephalometric variables ANB ($^\circ$), PAS (mm), and Linder-Aronson PNS-ad$_2$ (mm) between the two study groups defined as non-surgical positive
responders (n = 37) and surgical positive responders (n = 13). Mean differences were calculated by subtracting the surgical positive responder means from the non-surgical positive responder means (Table I).

Between non-surgical and surgical positive responders, the cephalometric variable ANB showed a mean difference of \(-1.61^\circ \pm 0.546^\circ\), 95% CI \((-2.71, -0.516)\), \(p\)-value = 0.005. The mean ANB for the group of non-surgical positive responders of \(4.66^\circ \pm 2.83^\circ\) was smaller than the mean ANB for the group of surgical positive responders of \(6.28^\circ \pm 1.04^\circ\).

Between non-surgical and surgical positive responders, the cephalometric variable PAS showed a mean difference of \(2.43 \text{ mm} \pm 0.793 \text{ mm}\), 95% CI \((0.820, 4.03)\), \(p\)-value = 0.004. The mean PAS for the group of non-surgical positive responders of \(11.32 \text{ mm} \pm 3.47 \text{ mm}\) was larger than the mean PAS for the group of surgical positive responders of \(8.89 \text{ mm} \pm 1.99 \text{ mm}\).

Between non-surgical and surgical positive responders, the cephalometric variable Linder-Aronson PNS-ad\(_2\) showed a mean difference of \(-2.78 \text{ mm} \pm 1.19 \text{ mm}\), 95% CI \((-5.17, -0.340)\), \(p\)-value = 0.023. The mean Linder-Aronson PNS-ad\(_2\) for the group of non-surgical positive responders of \(11.69 \text{ mm} \pm 3.27 \text{ mm}\) was smaller than the mean Linder-Aronson PNS-ad\(_2\) for the group of surgical positive responders of \(14.47 \text{ mm} \pm 4.69 \text{ mm}\).
In all of the positive responders (n=50), the Pearson correlation test did not show a statistically significant correlation between any of the cephalometric variables and the percentage change in the total PSQ-SRBD score from baseline.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>N</th>
<th>( \bar{x}, \text{SD} )</th>
<th>( \bar{x} \text{ Diff}, \text{SE} )</th>
<th>P-value</th>
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<tr>
<td>BMI (kg/m(^2))</td>
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<td>Change in PSQ from baseline (%)</td>
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<td>6.28 ± 1.04</td>
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<td>Surgical positive responders</td>
<td>13</td>
<td>6.23 ± 2.65</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAS (mm)</td>
<td>Non-surgical positive responders</td>
<td>37</td>
<td>11.32 ± 3.47</td>
<td>2.43 ± 0.793</td>
<td>0.004**</td>
</tr>
<tr>
<td></td>
<td>Surgical positive responders</td>
<td>13</td>
<td>8.89 ± 1.99</td>
<td></td>
<td></td>
</tr>
<tr>
<td>McNamara line (mm)</td>
<td>Non-surgical positive responders</td>
<td>37</td>
<td>6.92 ± 3.11</td>
<td>-1.76 ± 1.40</td>
<td>0.228</td>
</tr>
<tr>
<td></td>
<td>Surgical positive responders</td>
<td>13</td>
<td>8.68 ± 4.71</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*\(P < 0.05; **P < 0.01\)
### TABLE I (continued)
INDEPENDENT STUDENT'S T-TESTS BETWEEN NON-SURGICAL AND SURGICAL POSITIVE RESPONDERS

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>N</th>
<th>$\bar{x}$, SD</th>
<th>$\bar{x}$ Diff., SE</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PNS-ad$_2$ (mm)</td>
<td>Non-surgical positive responders</td>
<td>37</td>
<td>11.69 ± 3.27</td>
<td>-2.78 ± 1.19</td>
<td>0.023*</td>
</tr>
<tr>
<td></td>
<td>Surgical positive responders</td>
<td>13</td>
<td>14.47 ± 4.69</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PNS-ad$_1$ (mm)</td>
<td>Non-surgical positive responders</td>
<td>37</td>
<td>15.01 ± 4.81</td>
<td>-1.54 ± 1.48</td>
<td>0.304</td>
</tr>
<tr>
<td></td>
<td>Surgical positive responders</td>
<td>13</td>
<td>16.55 ± 3.82</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SNA (°)</td>
<td>Non-surgical positive responders</td>
<td>37</td>
<td>79.92 ± 3.87</td>
<td>-1.32 ± 1.24</td>
<td>0.291</td>
</tr>
<tr>
<td></td>
<td>Surgical positive responders</td>
<td>13</td>
<td>81.24 ± 3.74</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SNB (°)</td>
<td>Non-surgical positive responders</td>
<td>37</td>
<td>75.25 ± 3.21</td>
<td>0.274 ± 1.12</td>
<td>0.807</td>
</tr>
<tr>
<td></td>
<td>Surgical positive responders</td>
<td>13</td>
<td>74.98 ± 4.15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SN-Ba (°)</td>
<td>Non-surgical positive responders</td>
<td>37</td>
<td>133.26 ± 5.84</td>
<td>3.09 ± 1.95</td>
<td>0.119</td>
</tr>
<tr>
<td></td>
<td>Surgical positive responders</td>
<td>13</td>
<td>130.17 ± 6.57</td>
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<td></td>
</tr>
<tr>
<td>Total amount of expansion (mm)</td>
<td>Non-surgical positive responders</td>
<td>37</td>
<td>7.47 ± 1.47</td>
<td>0.473 ± 0.470</td>
<td>0.319</td>
</tr>
<tr>
<td></td>
<td>Surgical positive responders</td>
<td>13</td>
<td>7.00 ± 1.43</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*P < 0.05; **P < 0.01
Of the 58 subjects included in this study, 29 were identified as high risk for pediatric SRBD based on having a pre-RME total PSQ-SRBD scores ≥ 0.33. Of the 29 high-risk subjects, 23 were identified as positive responders. In subjects at high risk for pediatric SRBD, “positive responders” were defined as subjects who had post-RME total PSQ-SRBD scores that decreased to < 0.33 and by at least 25% below baseline. Of the 23 high-risk positive responders, 14 were non-surgical and 9 were surgical, as defined above.

Independent Student’s t-tests indicated statistically significant mean differences in the cephalometric variables facial axis (°) and PAS (mm) between the two study groups defined as high-risk non-surgical positive responders (n=14) and high-risk surgical positive responders (n=9). Mean differences were calculated by subtracting the high-risk surgical positive responder means from the high-risk non-surgical positive responder means (Table II).

The cephalometric variable facial axis (°) showed a mean difference of $4.19° \pm 1.47°$, 95% CI (1.14, 7.24), $p$-value $= 0.009$. The mean facial axis for the group of high-risk non-surgical positive responders of $85.21° \pm 3.80°$ was larger than the mean facial axis for the group of high-risk surgical positive responders of $81.02° \pm 2.72°$.

The cephalometric variable PAS (mm) showed a mean difference of $3.32 \text{ mm} \pm 1.21 \text{ mm}$, 95% CI (0.780, 5.86), $p$-value $= 0.013$. The mean for the group of high-
risk non-surgical positive responders of 12.42 mm ± 4.00 mm was larger than the mean for the group of high-risk surgical positive responders of 9.10 mm ± 1.73 mm.

In the high-risk positive responders (n=23), the Pearson correlation test did not show statistically significant correlation between any of the cephalometric variables and the percentage change in the total PSQ-SRBD score from baseline.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>N</th>
<th>$\bar{x}$, SD</th>
<th>$\bar{x}$ Diff, SE</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BMI (kg/m$^2$)</strong></td>
<td>High-risk non-surgical positive responders</td>
<td>14</td>
<td>16.59 ± 2.55</td>
<td>0.911 ± 1.00</td>
<td>0.373</td>
</tr>
<tr>
<td></td>
<td>High-risk surgical positive responders</td>
<td>9</td>
<td>15.68 ± 1.97</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age at start of treatment (years)</strong></td>
<td>High-risk non-surgical positive responders</td>
<td>14</td>
<td>6.55 ± 2.09</td>
<td>-1.12 ± 0.951</td>
<td>0.252</td>
</tr>
<tr>
<td></td>
<td>High-risk surgical positive responders</td>
<td>9</td>
<td>7.67 ± 2.42</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Change in PSQ from baseline (%)</strong></td>
<td>High-risk non-surgical positive responders</td>
<td>14</td>
<td>-61.02 ± 23.11</td>
<td>3.86 ± 9.05</td>
<td>0.674</td>
</tr>
<tr>
<td></td>
<td>High-risk surgical positive responders</td>
<td>9</td>
<td>-64.88 ± 17.59</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ANB (°)</strong></td>
<td>High-risk non-surgical positive responders</td>
<td>14</td>
<td>4.89 ± 2.55</td>
<td>-1.23 ± 0.794</td>
<td>0.137</td>
</tr>
<tr>
<td></td>
<td>High-risk surgical positive responders</td>
<td>9</td>
<td>6.12 ± 1.22</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Facial axis (°)</strong></td>
<td>High-risk non-surgical positive responders</td>
<td>14</td>
<td>85.21 ± 3.80</td>
<td>4.19 ± 1.47</td>
<td>0.009**</td>
</tr>
<tr>
<td></td>
<td>High-risk surgical positive responders</td>
<td>9</td>
<td>81.02 ± 2.72</td>
<td></td>
<td></td>
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<tr>
<td><strong>SN-MP (°)</strong></td>
<td>High-risk non-surgical positive responders</td>
<td>14</td>
<td>42.22 ± 4.10</td>
<td>-1.55 ± 2.03</td>
<td>0.455</td>
</tr>
<tr>
<td></td>
<td>High-risk surgical positive responders</td>
<td>9</td>
<td>43.77 ± 5.66</td>
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<td></td>
</tr>
<tr>
<td><strong>A/N ratio</strong></td>
<td>High-risk non-surgical positive responders</td>
<td>14</td>
<td>0.596 ± 0.102</td>
<td>0.059 ± 0.054</td>
<td>0.291</td>
</tr>
<tr>
<td></td>
<td>High-risk surgical positive responders</td>
<td>9</td>
<td>0.537 ± 0.158</td>
<td></td>
<td></td>
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<tr>
<td><strong>RPA (mm)</strong></td>
<td>High-risk non-surgical positive responders</td>
<td>14</td>
<td>4.95 ± 1.76</td>
<td>-0.728 ± 0.798</td>
<td>0.372</td>
</tr>
<tr>
<td></td>
<td>High-risk surgical positive responders</td>
<td>9</td>
<td>5.68 ± 2.04</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PAS (mm)</strong></td>
<td>High-risk non-surgical positive responders</td>
<td>14</td>
<td>12.42 ± 4.00</td>
<td>3.32 ± 1.21</td>
<td>0.013*</td>
</tr>
<tr>
<td></td>
<td>High-risk surgical positive responders</td>
<td>9</td>
<td>9.10 ± 1.73</td>
<td></td>
<td></td>
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<tr>
<td><strong>McNamara line (mm)</strong></td>
<td>High-risk non-surgical positive responders</td>
<td>14</td>
<td>6.03 ± 2.51</td>
<td>-2.46 ± 1.86</td>
<td>0.214</td>
</tr>
<tr>
<td></td>
<td>High-risk surgical positive responders</td>
<td>9</td>
<td>8.49 ± 5.21</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*P < 0.05; **P < 0.01
### TABLE II (continued)

INDEPENDENT STUDENT’S T-TESTS BETWEEN HIGH-RISK NON-SURGICAL AND SURGICAL POSITIVE RESPONDERS

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>N</th>
<th>$\bar{x}$, SD</th>
<th>$\bar{x}$ Diff., SE</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PNS-ad$_2$ (mm)</td>
<td>High-risk non-surgical positive responders</td>
<td>14</td>
<td>11.24 ± 3.15</td>
<td>-2.34 ± 1.91</td>
<td>0.245</td>
</tr>
<tr>
<td></td>
<td>High-risk surgical positive responders</td>
<td>9</td>
<td>13.58 ± 5.16</td>
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<tr>
<td>PNS-ad$_1$ (mm)</td>
<td>High-risk non-surgical positive responders</td>
<td>14</td>
<td>13.38 ± 4.74</td>
<td>-2.17 ± 1.83</td>
<td>0.250</td>
</tr>
<tr>
<td></td>
<td>High-risk surgical positive responders</td>
<td>9</td>
<td>15.54 ± 3.42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SNA (°)</td>
<td>High-risk non-surgical positive responders</td>
<td>14</td>
<td>80.01 ± 4.19</td>
<td>-1.09 ± 1.68</td>
<td>0.525</td>
</tr>
<tr>
<td></td>
<td>High-risk surgical positive responders</td>
<td>9</td>
<td>81.10 ± 3.46</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SNB (°)</td>
<td>High-risk non-surgical positive responders</td>
<td>14</td>
<td>75.12 ± 3.62</td>
<td>0.133 ± 1.61</td>
<td>0.935</td>
</tr>
<tr>
<td></td>
<td>High-risk surgical positive responders</td>
<td>9</td>
<td>74.99 ± 3.99</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SN-Ba (°)</td>
<td>High-risk non-surgical positive responders</td>
<td>14</td>
<td>134.28 ± 5.95</td>
<td>5.52 ± 2.70</td>
<td>0.054</td>
</tr>
<tr>
<td></td>
<td>High-risk surgical positive responders</td>
<td>9</td>
<td>128.76 ± 6.89</td>
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<td></td>
</tr>
<tr>
<td>Total amount of expansion (mm)</td>
<td>High-risk non-surgical positive responders</td>
<td>14</td>
<td>8.00 ± 1.64</td>
<td>1.00 ± 0.719</td>
<td>0.179</td>
</tr>
<tr>
<td></td>
<td>High-risk surgical positive responders</td>
<td>9</td>
<td>7.00 ± 1.75</td>
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</tr>
</tbody>
</table>

*P < 0.05; **P < 0.01
5. DISCUSSION

5.1 Discussion

In the study groups of positive responders, it is important to note the differences between subjects who underwent T&A and those who did not. While PSG is the gold standard for the diagnosis and quantification of OSAS in children, 90% of children have T&A performed for OSAS based on clinical criteria alone due to the cost, burden, and availability of PSG (Mitchell et al. 2015). The American Academy of Otolaryngology-Head and Neck Surgery guidelines “do not recommend routine PSG prior to T&A in otherwise healthy children with tonsil hypertrophy and SDB” (Roland et al. 2011). T&A is the first-line treatment for OSA secondary to adenotonsillar hypertrophy and a recent systematic review and meta-analysis described the benefit of T&A for the treatment of OSA in improving the quality of life of pediatric patients (Todd et al. 2017). A large, randomized trial by Thomas et al. showed that early T&A for OSAS improved parent-rated behavioral problems as compared to 7 months of watchful waiting with supportive care (Thomas et al. 2017).

In our study, it can be assumed that subjects who underwent T&A presented to their pediatricians and ENT physicians with severe symptoms of pediatric SRBD and hypertrophy of the adenoid and tonsillar soft tissues. When nasal obstructions are present, as in the case of adenotonsillar hypertrophy, the body compensates by altered head and mandible positions and tone of the orofacial and tongue muscles in order to facilitate nasal breathing. Persistence of the obstruction and continued
bodily adjustments to promote breathing may eventually induce morphological dentoskeletal modifications, which may be reversible if corrected in a timely manner. Numerous risk factors for pediatric SRBD have been identified including adenotonsillar hypertrophy, skeletal retrusion, increased lower facial height, increased total anterior facial height, decreased posterior airway space, obesity, asthma, exposure to tobacco smoke, low socioeconomic status, neuromuscular conditions, craniofacial anomalies, and macroglossia (Flores-Mir et al. 2013; Bozzini and Di Francesco 2016). While craniofacial characteristics and obesity are strongly influenced by ethnicity, the prevalence of OSA in Asian and Caucasian populations have been shown to be similar (R. W. W. Lee et al. 2010). Studies have shown that when matched for OSA severity, Caucasians had higher BMI and larger neck circumference while Chinese subjects showed craniofacial bony restriction (Lam et al. 2005; R. W. W. Lee et al. 2010). When compared to BMI- and height-matched Caucasian subjects, Asian men (Chinese, Japanese, and Korean) have been shown to exhibit the following: more severe OSA, shorter anterior cranial base lengths, decreased cranial base flexure (more acute), shorter midface, maxilla, and mandible lengths, elongated soft palates, increased maxillomandibular protrusion, inferiorly positioned hyoids, greater SNA, ANB, Y-Axis, and SN-PP angles, and smaller gonial angles and PAS measurements (R. W. W. Lee et al. 2010; Li et al. 2000). A 2017 study by Anderson et al. found that craniofacial patterns in Korean children who exhibit chronic snoring, mouth breathing, and adenotonsillar hypertrophy can be grouped into three characteristic clusters defined as follows: ‘five-eight years with skeletal Class I or mild Class II and hyperdivergent pattern, nine-12 years with Class
II and hyperdivergent pattern, and seven-eight years with Class III and hyperdivergent pattern” (Anderson et al. 2017). Relating to the surgical subjects in our study, it is possible that in addition to airway obstruction caused by enlarged lymphoid tissues as the primary indication for T&A, these subjects also presented with Class II skeletal relationships, vertical growth patterns, and smaller airway spaces.

The significant values reported in our study are comparable to published norms. Pirila-Parkkinen et al. studied 70 children aged 4.17-11.96 years who were referred to the Department of Otorhinolaryngology of Oulu University Hospital due to snoring and symptoms related to SRBD. 70 age- and gender-matched controls were included. Based on PSG findings, subjects with SDB were separated by severity into three groups: OSA, upper airway resistance syndrome (UARS), and snoring. The mean PAS in those with OSA was 12 mm as compared to 11.9 mm in non-obstructed controls. The mean ANB in the OSA group was 5.7° as compared to 4° in the control group. The mean PNS-ad$_2$ was 13.7 mm in the OSA group and 15.8 mm in the control group (Pirilä-Parkkinen et al. 2010).

The results of our study showed that positive responders who underwent T&A were more skeletally Class II as measured by the ANB angle (6.28° ± 1.04°) than those who did not undergo T&A (4.66° ± 2.83°). A recent study by Iwasaki et al. showed that the incidence of adenoid hypertrophy (grades 3 and 4) was 15.2% in Class II subjects (ANB > 5°) and 3.2% in Class III subjects (ANB < 1°) and that nasal
resistance was significantly greater in the Class II group (Iwasaki et al. 2017).

Similarly, studies have shown statistically significant higher ANB values in children with OSAS as compared to controls and that the ANB angle is predictive of OSA severity, significantly positively correlated with tonsillar hypertrophy grade, and negatively correlated with oropharyngeal area (Diouf et al. 2015; Ceylan and Oktay 1995; Flores-Mir et al. 2013; Sakamoto et al. 2016). Since the results of our study showed that subjects with higher ANB angles tended to be surgical patients, it is likely that these patients presented with more severe SRBD-related symptoms that led to ENT referral and subsequent T&A due to enlarged adenoids. Our study confirmed that surgical patients with residual symptoms further improved after treatment with RME. Because a Class II skeletal relationship identified on a lateral cephalogram is consistent with pediatric OSAS, the presence of this morphology should alert orthodontists and lead to further inquiry about SDB symptoms and if present, warrant a referral to an ENT for evaluation. As in the case of our study’s non-surgical subjects, identification of this variable and appropriate questioning related to SBD symptoms is particularly important in those with less severe Class II skeletal relationships. These patients may not be referred to ENTs due to less severe symptoms and/or T&A may not be indicated due to less prominent adenoid hypertrophy, but will likely benefit greatly from treatment with RME.

While the PAS measurement is not based on the size of the adenoid, a smaller PAS linear measurement is associated with more severe symptoms of SRBD. As in our findings, Alves et al. demonstrated that the pharyngeal airway space dimensions
measured on CBCT at various levels in awake upright children are larger in those with ANB angles from 2° - 5° as compared to those with ANB angles > 5°. This study concluded that PAS dimensions are affected by differences in anteroposterior skeletal patterns (Alves et al. 2012). According to Muto et al., PAS widths were largest in a prognathic group and smallest in a retrognathic group and when measured at the level of the base of the tongue were 12.8 mm and 8.3mm, respectively (Muto, Yamazaki, and Takeda 2008). El and Palomo showed that PAS was the smallest in Class II retrognathic subjects and largest in Class III prognathic subjects (El and Palomo 2013). These studies support the finding that people who are retrognathic or have high ANB angles often present with compromised airways (Alves et al. 2012; Muto, Yamazaki, and Takeda 2008; El and Palomo 2013).

In our study, subjects classified as high-risk positive responders who underwent T&A showed a lower mean facial axis angle than high-risk positive responders who did not undergo T&A. It is important to note that all of the positive responders at high-risk for pediatric SRBD, regardless of history of T&A, had facial axis angles less than 90°, which is indicative of a vertical growth pattern and Class II skeletal relationship. A study by Sato et al. showed a significantly lower facial axis in the surgical (T&A) + drug therapy group of 82.69° as compared to 86.02° in the non-surgical group which had undergone drug therapy alone (Sato et al. 2012). Comparatively, in our study, the mean facial axis in the high-risk surgical (T&A) positive responders was 81.02° and 85.21° in high-risk non-surgical positive responders. In a study by Muto et al., when the relationships between the PAS at the
levels of the uvula and base of the tongue and craniofacial morphology were evaluated, facial axis was shown to be significantly positively correlated with measures of PAS at the level of the uvula and base of the tongue in the group of subjects as a whole. In our study, of the high-risk positive responders, the non-surgical group had higher mean facial axis and PAS values than the surgical group. As with the ANB angle and PAS, a smaller facial axis should alert the orthodontist to further investigate the patient’s medical history related to SDB. Patients with severe vertical growth patterns may be more symptomatic and readily identified based on longer facial appearance and are therefore more frequently referred to ENTs for T&A. Orthodontists must also recognize those who are mild vertical growers who may have more subtle symptoms that require further inquiry to elicit, but may benefit greatly from RME.

In our study, Linder-Aronson PNS-ad₂ was larger in the surgical group, as was expected since the adenoid tissue was removed during T&A. Linder-Aronson utilized ad₁-pm and ad₂-pm in mm as indicators of sagittal depth of the airway through the nasopharynx at the level of the adenoid and showed a strong correlation between the results of posterior rhinoscopy and radiographic cephalometric measurements (Linder-Aronson 1970; Linder-Aronson and Leighton 1983).

The use of RME has been shown to alter craniofacial morphology and influence the soft tissues. In 2015, Fastuca et al. showed significant increases in
upper, middle, and lower airway volumes, increased oxygen saturations, and improved AHIs after treatment with RME as measured by CBCT and PSG. Middle and lower airway volumes at baseline significantly negatively correlated with oxygen saturation increases and therefore, improvement in respiratory performance is greater when baseline middle and lower airway volume are smaller (Fastuca et al. 2015). According to a consensus paper by McNamara et al., RME in growing patients induces opening of the midpalatal suture and subsequently widens the base of the nasal cavity, decreases nasal airway resistance, and improves breathing. Timely orthopedic treatment with RME can improve SRBD symptoms and prevent the development or persistence of craniofacial characteristics consistent with OSA (McNamara et al. 2015). Many have postulated that the anteroposterior linear gains were likely due to advancement of the tongue into the oral cavity as a result of the maxillary expansion in the transverse dimension (Vinha et al. 2016).

Our study has confirmed that RME leads to a reduction in SRBD symptoms as measured by the PSQ. Of the total 58 subjects, 50 (86.2%) qualified as positive responders and showed a 64.20% mean decrease in PSQ scores from baseline, while the 8 non-responders showed an 8.65% mean increase in PSQ scores from baseline following treatment with RME. Of the 29 subjects classified as high risk for pediatric SRBD, 23 (79.3%) qualified as positive responders and showed a 62.92% mean decrease in PSQ scores from baseline, while the six high-risk non-responders showed a 27.61% decrease in PSQ scores from baseline following treatment with RME. Regardless of a patient’s history of T&A, the majority of subjects experienced
parent-reported improvement of symptoms. Vast amounts of literature support the effects of RME in similar populations (Chang et al. 2013; Fastuca et al. 2015; Camacho et al. 2017; Pirelli, Saponara, and Guilleminault 2004, 2015; Quo, Hyunh, and Guilleminault 2017). Quo, Hyunh, and Guilleminault showed that the majority of children with SDB aged three to 14 years old had improved sleep scores and symptoms following bimaxillary expansion (Quo, Hyunh, and Guilleminault 2017). In addition, a 12-year annual follow-up study on 23 subjects using PSG and CT imaging confirmed the stability of RME for treatment of pediatric OSA (Pirelli, Saponara, and Guilleminault 2015).

The results of our study did not show statistically significant correlation between any of the cephalometric variables and the percentage change in the total PSQ-SRBD score from baseline. Studies have shown the difficulty in predicting response to treatment in patients with SRBD, in part due to the recurrence of symptoms and adenoid regrowth. Meta-analyses have reported that while T&A leads to significant symptomatic improvements in most cases of pediatric OSAS, the success rates are highly variable (24-100%) and 20-30% of children may exhibit residual symptoms (Bozzini and Di Francesco 2016; Brietzke and Gallagher 2006; Guilleminault et al. 2007). It is important to assess and identify the etiology of residual and recurrent symptoms in order to treat appropriately. Adenoid regrowth occurs at a rate of 1.3% to 26% depending on the method of treatment, though it is rarely accompanied by clinical manifestations (Babademez et al. 2017; Lesinskas and Drigotas 2009; Grindle et al. 2011; S. Y. Kim et al. 2013; M. J. Kim, An, and Chung
A 2013 study by Kim et al. evaluated 188 Korean children who had undergone coblation adenoidectomy and showed that 13.3% exhibited adenoid regrowth at one-year follow-up. Preoperative adenoid size was found to be larger in subjects who experienced regrowth and those who experienced regrowth had a significantly lower mean age than those who did not have regrowth (S. Y. Kim et al. 2013). Studies have shown that adenoid regrowth occurs more commonly in children younger than five years of age or in those who were treated with antibiotics postoperatively on numerous occasions (Lesinskas and Drigotas 2009). In addition, recurrent symptoms may be related to allergic rhinitis, deviation of nasal septa, or dentoskeletal deformities, such as narrow maxillary dental arches (Bozzini and Di Francesco 2016).

In summary, craniofacial characteristics have been identified as predisposing factors for SRBD, including skeletal retrusion, increased lower facial height, increased total anterior facial height, and decreased posterior airway space (Bozzini and Di Francesco 2016). Similarly, surgical subjects in our study had more severe Class II skeletal relationships, vertical growth patterns, and smaller posterior airway spaces compared to non-surgical subjects. The surgical subjects in this study were referred to the orthodontist by ENTs after T&A due to unresolved symptoms. Persistence of airway obstruction and continued bodily adjustments to promote breathing may induce further undesirable morphological dentoskeletal compensations. Regardless of history of T&A, patients with SRBD benefit greatly
from RME in terms of symptomatic improvements, which may allow for the reversal or decrease in severity of the associated dentoskeletal alterations.

It has been estimated that more than 80-90% of adults with OSAS remain undiagnosed. The true prevalence of undiagnosed OSA in the pediatric population remains unknown, but is thought to be even higher than that in the adult population (Finkel et al. 2009; Chervin et al. 2000; Holmes et al. 2017; Ishman et al. 2015). In patients who are Class II, have smaller PAS, or lower facial axis angles, regardless of the severity, orthodontists should inquire about sleep issues to elicit concerns from the parent. Recognizing associated craniofacial patterns, asking applicable questions, and referring to appropriate medical specialists may increase the likelihood that more children with SRBD will be identified and treated efficiently.

Due to frequent interactions with patients at monthly appointments and involvement in treating the facial skeleton and occlusion, orthodontists play a significant role in recognizing pediatric SRBD. Orthodontists regularly obtain records that are valuable in assessing risk including extraoral and intraoral photographs, 2D and 3D radiographic images, diagnostic impressions, and detailed medical histories, all of which are instrumental in identifying craniofacial morphologies and symptoms related to SRBD. The information gathered can be used as a screening tool to indicate to the orthodontist when a patient should be referred to an ENT or sleep physician. According to a systematic review by Major et al. in 2014, lateral cephalograms used in conjunction with a thorough medical history is
the best available approach for screening of adenoid hypertrophy by dentists (Major et al. 2014). Orthodontists should be aware that T&A is often performed at a young age and adenoid regrowth is possible. Therefore, when a patient in their early teens presents for orthodontic records and discloses a history of T&A, one must not assume that all SRBD symptoms have been resolved. In addition to skeletal assessments, the airway and tonsillar tissues on lateral cephalograms should be evaluated and sleep-related questions should be asked. It is crucial for the orthodontist to establish rapport with and educate local pediatricians and ENT physicians to facilitate efficient and accurate identification, referral, and treatment of patients with SRBD symptoms.

5.2 Limitations

The following limitations should be noted:

This study did not include an age- and gender-matched control group that did not undergo treatment with RME.

This study sample consisted of South Korean children only and therefore, it is not generalizable to other populations of age-matched subjects. A recent study with 700 children greater than two years of age found that 15.1% of subjects had SDB as measured by a 31-item Korean version of the PSQ (D. S. Kim, Lee, and Ahn 2017).
As previously described, the PSQ is a subjective parent-reported outcome measure. Furthermore, the PSQ used in this study contained 22 items translated into a Korean version of the survey, which had not yet been validated (Appendix B). The use of a translated and non-validated version of the PSQ may have influenced the meaning of the questions or parents’ understanding. Despite this, studies have shown the value in utilizing the PSQ as an assessment tool. In a recent study by Holmes et al., the PSQ was used to evaluate the prevalence of SRBD in children undergoing elective day surgery procedures. The results of the study led to the recommendation that the PSQ may be used to screen pediatric patients prior to surgery and may lead to the implementation of important intraoperative and postoperative modifications (Holmes et al. 2017).

The criteria outlined in Section 1.2 used to define positive responders in all subjects as well as in the subgroup of high-risk subjects was based off of a 2015 paper by Chervin et al., which studied children with OSA from the CHAT who were randomized to a watchful waiting group with 7-month follow-up. In this study, symptomatic resolution of childhood OSAS was defined by a “total PSQ-SRBD score ≥ 0.33 at baseline, < 0.33 at 7-month follow-up, and at least 25% below baseline at follow-up in addition to an AHI < 2 and obstructive apnea index (OAI) < 1” (Chervin et al. 2015). These cutoff points may have been overly stringent and the study may have shown different results had the response cut-offs been set differently.
The use of 2D lateral cephalograms only allows for measurements in the anteroposterior plane despite the intervention of the study being RME in the transverse dimension. Additionally, compressing 3D structures into 2D images can cause significant structural information to be lost (Y.-J. Kim et al. 2010; Aboudara et al. 2009). The use of CBCT would allow for reorientation of slices and production of anatomically accurate images and 3D reconstructions with 1:1 correlation free from magnification or distortion (Major, Flores-Mir, and Major 2006). However, Bronoosh & Khojastepour showed that pharyngeal airway area as measured on a lateral cephalogram is strongly correlated with volumetric data on CBCT images (Bronoosh and Khojastepour 2015). Additionally, Vizzotto et al. demonstrated a positive correlation in upper airway assessment between conventional 2D and CBCT reconstruction techniques (Vizzotto et al. 2012). Based on ease-of-use, availability, and lower cost and radiation doses, conventional 2D cephalometry has maintained its diagnostic role in orthodontics.

5.3 **Future Research**

It may be interesting to conduct this study with a larger sample size and with three-dimensional CBCT imaging in order to comprehensively assess linear, area, and volumetric airway measurements. In the absence of CBCT imaging, the inclusion of posteroanterior (PA) cephalometric radiographs and 3D study models to supplement lateral cephalograms in the assessment of transverse skeletal and dentoalveolar changes could enrich the findings of this study and increase the clinical applicability of the results. Finally, lateral cephalometric radiographs taken
after RME would be beneficial in order to analyze the post-treatment skeletal and airway changes in the AP dimension, such as forward movement of the mandible.
6. CONCLUSIONS

6.1 Conclusions

The findings of this study on a population with symptoms of pediatric SRBD showed that in positive responders, those who had undergone T&A had statistically significant higher mean ANB angles and Linder-Aronson PNS-ad₂ measurements and lower mean PAS measurements than those who did not undergo T&A. For SRBD high-risk positive responders, those who had undergone T&A had statistically significant lower mean facial axis angles and PAS measurements than those who did not undergo T&A. No statistically significant correlation was found between any of the cephalometric variables and the percentage change in the total PSQ-SRBD score from baseline.

In conjunction with a thorough medical history, baseline 2D lateral cephalometric variables, which are routinely assessed in orthodontic practice, may be implemented as a screening tool in determining response to RME. Early detection of SRBD and appropriate referrals to sleep medicine specialists for definitive diagnoses can help mitigate the associated comorbidities, including altered craniofacial and dentoskeletal morphologies, behavioral and cognitive delays, and cardiovascular disease.
CITED LITERATURE


Notice of Determination of Human Subject Research

February 3, 2017

Michele Equinda, DDS
Orthodontics
801 S, Paulina
M/C 841
Chicago, IL 60612
Phone: (516) 672-3267

RE: Protocol # 2017-0111
Cephalometric data and response to rapid maxillary expansion in children with sleep-disordered breathing

Sponsor: None

Dear Michele Equinda:

The UIC Office for the Protection of Research Subjects received your “Determination of Whether an Activity Represents Human Subjects Research” application, and has determined that this activity DOES NOT meet the definition of human subject research as defined by 45 CFR 46.102(f).

No protected health information will be provided to the principal investigator. All lateral cephalometric radiographs, Pediatric Sleep Questionnaire surveys, and descriptive information about the subjects will be de-identified prior to being provided to the PI by an orthodontist in private practice. A spreadsheet will include the following descriptive variables/baseline characteristics for the 60 subjects: age, gender, height, weight, history of adenoid surgery before RME, duration of RME activation, type of expansion appliance, presence or absence of posterior crossbite, and timing of post-treatment PSQ collection.

You may conduct your activity without further submission to the IRB.

Please be reminded that the private practice must address HIPAA requirements.

If this activity is used in conjunction with any other research involving human subjects or if it is modified in any way, it must be re-reviewed by OPRS staff.
### Korean Version of Pediatric Sleep Questionnaire

<table>
<thead>
<tr>
<th>arris</th>
<th>병력</th>
<th>오늘 날짜</th>
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<tbody>
<tr>
<td>enal</td>
<td>야드님</td>
<td>기름이 ....</td>
</tr>
<tr>
<td>romatic 비양을 고요한</td>
<td>양상 고요한</td>
<td>기름고 소리가 심한가요?</td>
</tr>
<tr>
<td>숫자가 거칠 적이 있나요?</td>
<td>숫자가 거칠 적이 있나요?</td>
<td></td>
</tr>
<tr>
<td>숫자는 것이 어려운 적이 있나요?</td>
<td>부모님이 ....</td>
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</tr>
<tr>
<td>야드님/파님이 낮 때 숨을 쉬는 것을 본 적이 있나요?</td>
<td>야드님/파님이.....</td>
<td></td>
</tr>
<tr>
<td>낮에 일으므로 숨을 쉬는 경향이 있나요?</td>
<td>야드님/파님이 낮에 일으므로 숨을 쉬는 경향이 있나요?</td>
<td></td>
</tr>
<tr>
<td>아침에 일어나면서 일안이 떨라있나요?</td>
<td>아침에 일어나면서 일안이 떨라있나요?</td>
<td></td>
</tr>
<tr>
<td>자고 일어나면 젖대가 떨어지는 경우가 있나요? (아뇨중)</td>
<td>자고 일어나면 젖대가 떨어지는 경우가 있나요? (아뇨중)</td>
<td></td>
</tr>
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<td>가문지 않은 (unfreshed) 채 깨내요?</td>
<td>가문지 않은 (unfreshed) 채 깨내요?</td>
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<tr>
<td>낮에 빠른 하요?</td>
<td>낮에 빠른 하요?</td>
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<td>학교 선생님이 학교에서 존대하고 야기한 적이 있나요?</td>
<td>학교 선생님이 학교에서 존대하고 야기한 적이 있나요?</td>
<td></td>
</tr>
<tr>
<td>출생 이후 키가 평균에서 많이 벗어나 적게 자란 적이 있나요?</td>
<td>출생 이후 키가 평균에서 많이 벗어나 적게 자란 적이 있나요?</td>
<td></td>
</tr>
<tr>
<td>체중이 많이 나가요?</td>
<td>체중이 많이 나가요?</td>
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<tr>
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<th>Yes</th>
<th>No</th>
<th>Don’t Know</th>
</tr>
</thead>
<tbody>
<tr>
<td>야드님/파님이 가끔 .......</td>
<td>아니다 &amp; 조금 그렇다</td>
<td>아니다 &amp; 조금 그렇다</td>
<td>아니다 &amp; 조금 그렇다</td>
</tr>
<tr>
<td>다른 사람이 직접 말할 때 경청하지 않는 것처럼 보이요?</td>
<td>아니다 &amp; 조금 그렇다</td>
<td>아니다 &amp; 조금 그렇다</td>
<td>아니다 &amp; 조금 그렇다</td>
</tr>
<tr>
<td>지시/임무를 체계하며 완수하는 것을 어려워요?</td>
<td>아니다 &amp; 조금 그렇다</td>
<td>아니다 &amp; 조금 그렇다</td>
<td>아니다 &amp; 조금 그렇다</td>
</tr>
<tr>
<td>외부의 자극에 의해 쉽게 산만해요?</td>
<td>아니다 &amp; 조금 그렇다</td>
<td>아니다 &amp; 조금 그렇다</td>
<td>아니다 &amp; 조금 그렇다</td>
</tr>
<tr>
<td>손발을 가만히 두지 못하거나 의자에 앉아서도 몸을 끌지락거리요?</td>
<td>아니다 &amp; 조금 그렇다</td>
<td>아니다 &amp; 조금 그렇다</td>
<td>아니다 &amp; 조금 그렇다</td>
</tr>
<tr>
<td>“있음없이 활동하거나” 미치 “없음없이 활동하는 것”처럼 행동하요?</td>
<td>아니다 &amp; 조금 그렇다</td>
<td>아니다 &amp; 조금 그렇다</td>
<td>아니다 &amp; 조금 그렇다</td>
</tr>
<tr>
<td>다른 사람의 활동(예를 들면 대화, 게임)을 방해하고 간섭하요?</td>
<td>아니다 &amp; 조금 그렇다</td>
<td>아니다 &amp; 조금 그렇다</td>
<td>아니다 &amp; 조금 그렇다</td>
</tr>
</tbody>
</table>

**TOTAL**
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PUBLICATIONS:


Shi C, Hohl TM, Leiner I, Equinda MJ, Fan X, Pamer EG. Ly6G+ neutrophils are dispensable for defense against systemic...