THE EFFECTS OF GRAVITY AND SCAR CONTRACTURE ON POST-SURGICAL TISSUE CHANGES AND SPEECH OUTCOMES FOLLOWING PHARYNGOPLASTIES

by

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Following cleft palate repair, approximately 20% of patients continue to display velopharyngeal dysfunction (VPD) and require secondary surgery. Those with VPD are more likely to develop aberrant speech errors, affecting communication abilities across the lifespan. The goal of secondary surgery is to create a narrowing of the velopharyngeal space that allows for improved speech and resonance, but avoids airway morbidity. To reduce failure rate, inserting the sphincter pharyngoplasty flaps to the height of attempted velopharyngeal contact has been advised. However, surgical failure is prevalent and post-operative assessment frequently reveals low-set pharyngoplasties. It remains unknown the extent to which post-operative tissue migration occurs and how this migration influences speech outcomes. There is a need to examine the initial placement and subsequent movement of the pharyngoplasty within the nasopharyngeal airway.

A series of investigations were designed to explore and validate the use of imaging methodologies to assess post-surgical tissue changes secondary to pharyngoplasties and their effects on speech outcomes. Study I aimed to validate the use a reference line to quantify the vertical distance between the height of velopharyngeal closure and C1 as well as to provide data for how this distance changes across a typically developing child population. Study II focused on

the application of data provided from Study I to a disordered population which included varying diagnoses of cleft palate from childhood through adolescence. Study III developed a method to volumetrically assess the nasopharyngeal airway utilizing 3D MR imaging and computer modeling. Results from this study provided insight into the integration and applicability of the use of 3D visualization of the velopharyngeal mechanism for identification of post-surgical changes in subjects following pharyngoplasty. Study IV applied the methodologies established in studies I, II, and III to comprehensively examine post-surgical tissue changes relative to the bony cervical landmarks and correlate post-surgical tissue changes to speech outcomes following pharyngoplasties.

Data from study IV confirms that inferior tissue displacement of the pharyngoplasty occurs post-operatively. Significant differences were present between the initial site of pharyngoplasty tissue insertion and the final pharyngoplasty location 2-4 months post-operatively. Pharyngoplasties located below the level of C1 resulted in poorer perceptual and quantitative measures of speech. Gravity, scar contracture, and patient-specific variables likely interact, impacting the final post-operative pharyngoplasty location.

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CHAPTER 1

INTRODUCTION

Clefting is associated with more than 400 known syndromes and non-syndromic prevalence rates reach an additional 7,400 live births per year (Parker et al., 2010; Winter & Baraitser, 1987). These palatal or velopharyngeal anomalies can lead to velopharyngeal dysfunction (VPD) and cause difficulties with speech and resonance affecting communication abilities across the lifespan. Cleft palate is the most common cause of VPD. Approximately 20-30% of patients following primary cleft palate repair continue to display VPD and require secondary surgery to eliminate hypernasal speech (Bicknell, McFadden, & Curran, 2002). Those with VPD are more likely than those without hypernasal speech to develop aberrant speech and compensatory errors post-surgically (Riski, 1979).

The most common surgical methods to treat VPD are sphincter pharyngoplasty and pharyngeal flap (Cable, Canady, Karnell, Karnell, & Malick, 2004; Sloan, 2000). Pharyngoplasties are typically performed between 2-17 years of age when VPD is documented. The goal of surgery is to create a narrowing of the velopharyngeal space that allows velopharyngeal closure for speech and improves resonance, but avoids airway morbidity. Thus, revision to the secondary surgery is indicated when a child develops airway complications or shows no improvement in resonance (Sloan, 2000; Sommerlad et al., 1994). An estimated 13-23% of patients will have a failed pharyngoplasty that will require an additional surgical revision (Kasten, Buchman, Stevenson, & Berger, 1997; Losken, Williams, Burstein, Malick, & Riski, 2003; Witt, Marsh, Marty-Grames, & Muntz, 1995). Crockett et al. (1988) reported a significant failure rate and discussed failure in terms of three specific areas: incomplete methods of pre-operative assessment, inadequate choice of post-operative procedure, and uncontrolled wound healing.

Riski et al. (1992) observed the primary cause of failed pharyngoplasty was insertion of the pharyngeal flap below the point of attempted velopharyngeal contact during speech production. To reduce failure rate, Riski et al. (1984) demonstrated the use of pre-surgical lateral radiographs during sustained phonation to determine the level of attempted velopharyngeal closure during speech relative to the first cervical vertebra. The first cervical vertebra was used to provide an intra-operative landmark so that the pharyngoplasty is inset above this palpable landmark. Carlisle et al. (2011) discusses routinely placing the myomucosal flaps "as high in the nasopharynx as feasibly possible", oftentimes resecting a portion of adenoid tissue. Others have also advised elevating the height of insertion as high as possible (Jackson & Silverton, 1977; Roberts & Brown, 1983) to increase success rate. Although clinically this approach is feasible, it provides no insight into what constitutes a position that is "high enough" for proper velopharyngeal function. Furthermore, it provides no quantitative method to guide surgical planning and determine prognosis.

Riski et al. (1984), in a report on their institutions 15-year experience, suggested a rationale for tailoring the height of flap insertion. The height of attempted velopharyngeal contact was pre-operatively identified relative to the anterior tubercle of the first cervical vertebrae. Palpation of this landmark intraoperatively assists in identifying the point that the flaps ideally should be inserted based on the predetermined height of velopharyngeal closure. Studies, however, have failed to quantify the optimal level of insertion and demonstrate a clear intra-operative approach for ensuring proper placement. In addition, due to unknown factors such as mobility of the pharyngoplasty post-surgically and the effects of scarring or growth on outcome, optimal insertion height may be further under-assessed. If the point of attachment to the pharyngeal wall changes, misalignment tissue may tether the sphincter flaps downward (Friedman, Haines, Coston, Lett, & Edgerton, 1992). These factors may play a role in the failure rate and may be associated with the low-set pharyngoplasties that post-operative assessment tends to reveal.

A series of investigations were designed to explore and validate the use of our research methodology to assess post-surgical tissue changes secondary to pharyngoplasties and their effects on speech outcomes. **Study I** aimed to validate the use a reference line to quantify the vertical distance between the height of velopharyngeal closure and C1 as well as to provide data for how this distance changes across a typically developing child population. **Study II** focused on the application of data provided from Study I to a disordered population which included varying diagnoses of cleft palate from childhood through adolescence. **Study III** developed a method to volumetrically assess the nasopharyngeal airway utilizing 3D MR imaging and computer modeling. Results from this study provided insight into the integration and applicability of the use of 3D visualization of the velopharyngeal mechanism for identification of post-surgical changes in subjects following pharyngoplasty. **Study IV** assessed post-surgical tissue changes relative to the bony cervical landmarks and the correlation of pre- and post-surgical anatomy to speech outcomes in a larger sample of children using an established child-friendly MRI and 3D modeling protocol, with no sedation. The series of investigations are further described below:

Study I: Does the distance between the level of velopharyngeal closure and C1 change in typically developing children as they age?

Mason, K.N., Perry, J.L., Riski, J.E., & Fang, X. (2016). Age-Related Changes Between the Level of Velopharyngeal Closure and the Cervical Spine. *Journal of Craniofacial Surgery*, *27*(2), 498.

The primary focus of this study was to assess age-related changes in the vertical distance of the estimated level of velopharyngeal closure in relation to a prominent landmark of the cervical spine: the anterior tubercle of cervical vertebra 1 (C1). Midsagittal anatomic magnetic resonance images were examined across 51 participants with normal head and neck anatomy between 4 and 17 years of age. Results indicate that age is a strong predictor ($p = 0.002$) of the vertical distance between the level of velopharyngeal closure relative to C1. Specifically, as age increases, the vertical distance between the palatal plane and C1 becomes greater resulting in the level of velopharyngeal closure being located higher above C1 (range 4.88-10.55 mm). Results of this study provide insights into the clinical usefulness of using C1 as a surgical landmark for placement of pharyngoplasties in children with repaired cleft palate and persistent hypernasal speech. Clinical implications and future directions are discussed.

Study II: Is there a similar pattern of change between the level of velopharyngeal closure and C1 in children with differing types of cleft palate and non-cleft VPD?

Mason, K.N., Riski, J.E., Perry, J.L. (in press). Changes in the Level of Velopharyngeal Closure Relative to the Cervical Spine from Infancy through Adolescence in patients with cleft and non-cleft VPD. *Cleft Palate Craniofacial Journal.*

Surgical treatment of VPD is often necessary following primary palatoplasty. While many studies have assessed the age at which surgical repair is most successful, underlying anatomical changes related to the level of velopharyngeal closure (and landmarks on the cervical spine) are less explicit. Palpation of C1 is often utilized as an intraoperative landmark for placement of the pharyngoplasty. Lateral cephalograms were analyzed in non-syndromic patients who underwent primary palatoplasty. Regression analysis and analysis of covariance were completed to determine how age and cleft type impact underlying cervical and velopharyngeal measures. Age and cleft type were significant predictors of the distance between the level of velopharyngeal closure and C1. Those with greater severity of clefting demonstrated larger distances between the level of velopharyngeal closure and C1. Compared to normative data, children with cleft palate have significantly larger distances between the palatal plane and C1. The level of velopharyngeal closure above C1 was observed to range from 3.6 mm to 12.6 mm across cleft populations. Due to differences in the level of velopharyngeal closure across cleft types, it is necessary to quantify pre-operatively the vertical distance between the palatal plane and palpable intraoperative landmark, C1, to determine the appropriate level of pharyngoplasty insertion.

Study III: Do post-surgical differences in the nasopharyngeal airway exist following primary palatoplasty for patients with differing cleft types?

Mason, K.N., & Perry, J.L. (2016). Relationship Between Age and Diagnosis on Volumetric and Linear Velopharyngeal Measures in the Cleft and Noncleft Populations. *Journal of Craniofacial Surgery*.

Patency of the nasopharyngeal airway post-operatively is crucial for an adequate breathing portal. Surgical goals focus on narrowing the posterior pharynx at the velopharyngeal port. A balance must be created between the anatomy needed for breathing and that needed for speech. The purpose of this study was to create a 3D volumetric segmentation from magnetic resonance images (MRI) of the nasopharyngeal space and adenoid tissue and to examine the relationship between nasopharyngeal volume, adenoid volume, and linear measures of the velopharyngeal structures, pharynx, and vocal tract in children with and without cleft palate. A total of 24 participants including 18 typically developing children (4-8 years of age) and 6 children (4-8 years of age) with varying degrees of cleft palate were imaged using MRI. Linear and volumetric variables varied significantly based on age. Overall, nasopharyngeal volume demonstrates a modest increase with age. Nasopharyngeal volume was positively correlated with age ($p = 0.000$), oronasopharyngeal volume ($p = 0.000$), velar length ($p = 0.018$), and velar thickness ($p = 0.046$). These variables tend to increase together. Differences in nasopharyngeal volume between groups (bilateral cleft lip and palate, submucous cleft lip and palate, unilateral cleft lip and palate (UCLP), and noncleft) were statistically significant ($p = 0.007$). Participants with bilateral cleft lip and palate demonstrated greater nasopharyngeal volumes than those with UCLP and submucous cleft palate. Significant differences were noted across differing cleft types. Thus, nasopharyngeal volume was notably larger in patients with more severe cleft types. This difference in airway volume is likely tied to speech and breathing outcomes. However, speech data were not present in the population studied and this relationship has yet to be verified.

Study IV: Do external factors (such as scar contracture and gravity) affect the placement of the tissue for the pharyngoplasty post-surgically? If so, how does this affect speech outcomes?

To our knowledge, no studies have assessed post-surgical tissue changes of the pharyngoplasty relative to the nasopharynx or vertebral column. Furthermore, critical barriers (radiation exposure) have limited our ability to examine the post-surgical nasopharyngeal airway. It is likely that the external forces of gravity and scar tissue development cause the pharyngoplasty to migrate inferiorly to a more unfavorable location compared to the placement during surgery. The amount of inferior displacement and the effects on speech outcomes, however, is unknown. The overarching aims of this study are to examine the use of pre-operative cephalometric analyses and post-operative MRI to quantify the placement of the pharyngoplasty, visualize the nasopharyngeal airway, and examine the effect of inferior tissue migration on speech outcomes. This study is designed to bring together methodology demonstrated in studies I, II, and III to comprehensively examine the effect of external factors on a pharyngoplasty among children with VPD.

Data from the present study provides insights into the effect of external forces on the final positioning of the pharyngoplasty and to examine post-surgical speech outcomes relative to the placement of the pharyngoplasty. It is well established that pharyngoplasties positioned below the level of palatal plane are suboptimal and often result in a surgical revision. A notable limitation to prior investigations is the inability to quantify the migration of the flap over time. The advancements in MRI allow for safe, non-invasive techniques to provide detailed imaging of the velopharyngeal mechanism without exposing a child to radiation. Utilizing these advancements, this study is the first to evaluate the stability of pharyngoplasty insertion over time. Data obtained directly affect the clinical decision making processes and provide insight for improved outcomes. Our preliminary studies describe the methodological approaches that are anticipated. The following aims and hypotheses are addressed in this study.

STUDY AIMS

Aim I: To demonstrate the use of pre-operative cephalometric and MRI analyses using visualization software to quantify the location of the level of velopharyngeal closure relative to C1.

Cephalometric images, taken as part of the clinical protocol, will be imported into visualization software to quantify the location of velopharyngeal closure relative to C1. These values will be used to guide surgical placement of the pharyngoplasty intra-operatively. Magnetic resonance imaging (without sedation) will be used 1-3 days post-operatively to determine the extent to which the surgeon was able to use these measures to guide placement at or above the level of velopharyngeal closure.

Hypothesis 1. The recommended placement of the pharyngoplasty will, on average, be greater than 5 mm above the first cervical vertebrae.

Rationale. The palatal plane is often difficult to determine intraoperatively due to the supine nature of surgical patient positioning and changes to the functional level of velopharyngeal closure secondary to the use of a Dingman retractor. Thus, C1 is an easily palpable landmark along the posterior wall. Pre-operative measurement of the vertical distance can assist in appropriate estimation of placement intraoperatively above C1 along the posterior pharyngeal wall. Pre-operative recommendations often suggest “placing the pharyngoplasty at or above C1 at the level of attempted velopharyngeal closure” (Riski et al., 1984). Our preliminary studies indicated that the level of velopharyngeal closure in normal subjects fell between 4.88mm to 10.55mm above C1. Thus, we anticipate that pre-operative recommendations will be greater than 5mm above C1.

Aim II: To determine the extent of inferior migration of pharyngoplasty relative to C1 and assess the impact of tissue migration on speech outcomes.

Subjects will complete an MRI scan post-surgically (within1-3 days post-operatively) and a clinical cephalometric radiograph 2-4 months post-surgically. Visualization software will be used to analyze a midsagittal image to determine the position of the pharyngoplasty relative to the level of velopharyngeal closure and quantify changes that occur between the two post-surgical time points. Measures of cervical growth will be used to remove the effect of growth between time points, if noted. Pre- and post-operative speech data will be analyzed relative to the final pharyngoplasty position.

Hypothesis 2. The site of the pharyngoplasty will be at or above C1 immediately following surgical placement.

Rationale. Post-operative studies have demonstrated low-set pharyngoplasty despite attempts to place the pharyngoplasty high in the nasopharynx (Riski, Ruff, Georgiade, Barwick, & Edwards, 1992). Attempts to place the pharyngoplasty above the level of closure resulted in an 84-86% success rate (Pryor et al., 2006; Riski et al., 1984). Placement below the attempted level of velopharyngeal closure is commonly related to poor surgical outcomes with failure rates as high as 32.35% (Riski et al., 1984; Riski et al., 1992). It is unknown if placement of the pharyngoplasty was positioned higher intra-operatively or if significant migration of the flap occurs with time following post-operative healing of the pharyngoplasty. By obtaining measures immediately post-operatively, quantification of the initial placement and migration will be possible to assess.

Hypothesis 3. The level of insertion of the pharyngoplasty relative to C1 will be significantly lower than that observed immediately post-operatively when measured two to four months post-operatively.

Rationale. Pryor et al. (2006) found that scar contracture may cause linear shortening of the vertical donor scars, potentially displacing the pharyngoplasty inferiorly. However, no studies have quantified this movement. Utilizing measures obtained from hypothesis 2, quantification of the post-operative movement of the pharyngoplasty will be obtained. This will allow for comparison of post-surgical migration of the pharyngoplasty.

Hypothesis 4. Speech outcomes (nasometry scores) will be higher for individuals who demonstrate a post-operative pharyngoplasty position below the level of velopharyngeal closure.

Rationale. The level of velopharyngeal closure correlates to the palatal plane (Mason et al., 2016; Satoh et al., 1999). When the point of pharyngoplasty attachment to the pharyngeal wall changes misalignment of the palate and the pharynx may tether the sphincter flaps downward (Friedman et al., 1992). It is hypothesized that factors may play a role in the failure rate and be associated with poor speech outcomes and low-set pharyngoplasties that post-operative assessment tends to reveal.

Aim III: To quantify dimensions of the post-operative 3D nasopharyngeal airway and assess factors that show trends in influencing post-surgical tissue location.

Utilizing the post-operative MRI scan, images will be imported into visualization software and structures will be segmented. Measures of pharyngoplasty volume, tissue edema, and velopharyngeal variables will be assessed along with pharyngoplasty dimensions.

Hypothesis 5. The factors of cleft type, age, race, or velopharyngeal dimensions will be predictive of the amount of tissue displacement observed post-operatively.

Rationale. Visualization of the post-operative airway will provide information on three dimensional post-operative tissue changes. Causes of post-operative tissue changes can result from contraction of the nasopharynx around the tissue (Thurston, Larson, Shanks, Bennett, & Parsons, 1980). A smaller post-operative nasopharyngeal space, while beneficial for speech, often compromises breathing (Fukushiro, Zwicker, Genaro, Yamashita, & Trindade, 2013). Three dimensional visualization of the airway post-operatively will allow for improved assessment of initial tissue placement on post-operative pharyngoplasty location.

PRODUCTS OF DISSERTATION

Publications

Mason KN, Perry JL, Riski JE, & Fang, X. (2016). Age-Related Changes Between the Level of Velopharyngeal Closure and the Cervical Spine. *Journal of Craniofacial Surgery, 27*(2), 498.

Mason KN, Riski JE, Perry JL. (in press). Changes in the Level of Velopharyngeal Closure Relative to the Cervical Spine from Infancy through Adolescence in patients with cleft and non-cleft VPD. *Cleft Palate/Craniofacial Journal.*

Mason KN & Perry JL. (2016). Relationship Between Age and Diagnosis on Volumetric and Linear Velopharyngeal Measures in the Cleft and Noncleft Populations. *Journal of Craniofacial Surgery*.

Mason KN, Riski JE, Williams JK, Jones, R, Fang X, Perry JL. The effects of gravity and scar contracture on post-operative pharyngoplasty tissue location and speech outcome. Potential manuscript to be submitted to the *Cleft Palate/Craniofacial Journal.*

Mason KN, Riski JE, Williams JK, Jones, R, Ellis CE, Fang X, Perry JL. Factors influencing post-operative tissue migration of the sphincter pharyngoplasty. Potential manuscript to be submitted to *Plastic and Reconstructive Surgery.*

Grant Proposals & Funding Awards

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CHAPTER 2

LITERATURE REVIEW

This review of the literature presents pertinent information associated with the anatomy of cleft palate as well as primary and secondary surgical approaches used to treat velopharyngeal dysfunction (VPD). Current research related to surgical outcomes and relevant assessment through imaging modalities is summarized.

Incidence of Cleft Palate

Approximately 2,650 infants are born with a cleft palate and 4,440 infants are born with a cleft lip with or without a cleft palate in the US annually (Parker et al., 2010). Isolated clefts that occur in the absence of other birth defects are the most common form of birth defect observed in the US. Further, clefting is associated with more than 400 known syndromes (Winter & Baraitser, 1987). The prevalence rate of cleft palate has been reported to range from 0.97 – 1.47 per 1,000 live births (Golalipour, Mirfazeli, & Behnampour, 2007; IPDTOC Working Group, 2011). Cleft palate and velopharyngeal anomalies can lead to VPD and cause difficulties with speech and resonance affecting communication abilities across the lifespan. The purpose of this review is to outline the anatomical basis of clefting and associated speech difficulties as they relate to surgical intervention for patients with cleft palate.

Muscles Affected in Clefting

There is a significant amount of literature regarding the muscles affected in clefting. These muscles are subsequently involved in velopharyngeal function for speech (Abe et al., 2004; Huang, Lee, & Rajendran, 1997; Kuehn, Ettema, Goldwasser, Barkmeier, & Wachtel, 2001; McKerns & Bzoch, 1970; Perry, 2011a). Muscles commonly affected by clefting, referred to as velopharyngeal muscles, include the levator veli palatini, palatoglossus, paltopharyngeus, superior pharyngeal constrictor, tensor veli palatini and the salpingopharyngeus (Dickson & Dickson, 1972; Kuehn, 1979; Perry, 2011a; Skolnick, McCall, & Barnes, 1972). The musculus uvulae is additionally cited in the literature (Boorman & Sommerlad, 1985; Huang et al., 1997). Thus, clefting of the palate and absence of the palatal aponeurosis is reported to affect the below musculature.

Levator veli palatini. The levator veli palatini (LVP) arises from the apex of the petrous portion of the temporal bone and courses downward, medially, and anteriorly to insert into the soft palate. The LVP is innervated by the pharyngeal branch of the vagus nerve via the pharyngeal plexus (cranial nerve X) (Nishio, Matsuya, Machida, & Miyazaki, 1976; Perry, 2011a). When contracted, the LVP is the primary muscle for palatal elevation, bringing the soft palate into contact with the posterior pharyngeal wall to assist is closure between the oral and nasal cavities. This is necessary for appropriate production of oral and nasal consonants (Zemlin, 1998).

Palatoglossus muscle. The palatoglossus muscle (PG) originates from the inferior surface of the palatine aponeurosis. The muscle then travels inferiorly to insert underneath the posterior portion of the tongue, forming the bulk of the palatoglossal arch (anterior faucial pillars) (Tachimura, Ojima, Nohara, & Wada, 2005). It is innervated by the pharyngeal branch of the vagus nerve via the pharyngeal plexus (cranial nerve X) (Perry, 2011a). The PG may depress the velum, or when the velum is fixed, it may raise the lateral and posterior portions of the tongue. When contracted, the PG can also act as a sphincter and bring the palatoglossal arches closer together (Zemlin, 1998). The PG may further be involved in the regulation of swallowing from the oral to the pharyngeal phase (Tachimura et al., 2005).

Palatopharyngeus. The palatopharyngeus muscle (PP) contains both longitudinal and transverse muscle fibers. The longitudinal fibers originate from the palatine aponeurosis and the median line of the soft palate. The transverse fibers rest between the superior constrictor of the pharynx and the faucial arch (Sumida, Yamashita, & Kitamura, 2012). The PP is innervated by the pharyngeal branch of the vagus nerve (cranial nerve X) (Nishio et al., 1976; Perry, 2011a). The PP guides the bolus of food into the lower pharynx during deglutition, and it may raise the larynx or tilt the thyroid cartilage forward during phonation (Zemlin, 1998). The longitudinal PP plays a critical role in the clearance of food residue after deglutition to avoid overflow aspiration, and also plays a role in oral speech sounds. The longitudinal fibers of the PP are reported to elevate the pharynx, depress the soft palate, and pull the lateral pharyngeal walls medially. The transverse fibers of the PP primarily elevate the pharynx and depress the velum. Thus, the PP muscle acts as an antagonist to the levator muscle (Moon, Smith, Folkins, Lemke, & Gartlan, 1994; Seaver & Kuehn, 1980; Trigos, Ysunza, Vargas, & Vazquez, 1988). It is reported to additionally function as a sphincter when closing the pharyngeal isthmus (Sumida et al., 2012).

Superior pharyngeal constrictor. The superior pharyngeal constrictor (SPC) begins in portions of the pterygomandibular aponeurosis, medial pterygoid plate, mylohyoid line, and the glossopharyngeus. The muscle fibers continue posteriorly to insert into the pharyngeal raphe. The SPC, the uppermost portion of the pharyngeal tube, forms the lateral and posterior portions of the nasopharynx and the posterior wall of the oropharynx. The SPC is innervated by the vagus nerve (cranial nerve X) through the pharyngeal branch (Perry, 2011a). The SPC, primarily functions together with the middle and inferior constrictor muscle to aid in deglutition of the bolus. Its contracting motion pulls the pharyngeal wall forward while decreasing the width of the pharynx to move the bolus downward (Ashley, Sloan, Hahn, & Miethke, 1961; Bell-Berti, 1976).

Additionally, some fibers of the SPC have an attachment to the velum and therefore may assist in retraction of the velum (Kuehn, 1979). Calnan (1957) reported that horizontal fibers may further contribute to the formation of a Passavant's ridge, if present. Due to orientation of the muscle fibers and velar attachment, the SPC may also contribute to circular velopharyngeal closure patterns (Perry, 2011a).

Tensor veli palatini. The tensor veli palatine (TVP) is a thin, fan shaped muscle that arises from the scaphoid fossa, the spine of the sphenoid bone, and the lateral side of the Eustachian tube. It then travels inferiorly and anteriorly to wind around the pterygoid hamulus and then medially into the velum where it fans into the palatal aponeurosis and attaches to the horizontal plate of the palatine bone (hard palate) (Schönmeyr & Sadhu, 2014). The TVP is innervated by the trigeminal nerve (cranial nerve V) (McFarland, 2015). The TVP dilates the Eustachian tube and plays a role in velar tightening (Schönmeyr & Sadhu, 2014). Histological observations have shown that the hamulus acts as a pulley to assist the TVP in tensing the palatine aponeurosis and potentially adding stiffness to the anterior velum. However, the TVP does not assist in palatal elevation or velopharyngeal closure. The TVP is important for auditory tube function and ventilation of the tympanic cavity. Poor Eustachian tube function can lead to otitis media with effusion, hearing loss, and in turn, speech problems (Abe et al., 2004).

Salpingopharyngeus muscle. The salpingopharyngeaus muscle (SP) originates at the apex of the medial cartilaginous lamina at the opening of the Eustachian tube. The muscle courses vertically with the palatopharyngeus muscle. Some fibers insert directly into the palatopharyngeus while others terminate at the salpingopharyngeal fold and merge within the walls of the pharynx. It is innervated by the pharyngeal branch of the vagus nerve (cranial nerve X) (Perry, 2011a). The function of the SP is debated, but it potentially draws the lateral walls of the pharynx upward and medially and works with other muscles to open the Eustachian tube (McMyn, 1940; Zemlin, 1998). The size and presence of the muscle has been reported to vary across individuals (Dickson & Dickson, 1972). Thus, the SP may not significantly impact velopharyngeal closure. When present, however, the muscle may assist with superior movement of the lateral pharyngeal walls (Perry, 2011a).

Musculus uvulae. Originating at the palatine aponeurosis, the musculus uvulae (MU) is the only intrinsic velopharyngeal muscle. The MU courses posteriorly from its origin along the nasal surface of the velum (Azzam & Kuehn, 1977). The MU receives its nerve supply from the pharyngeal branch of the vagus nerve (cranial nerve X) and functions to add bulk and stiffness on the nasal surface of the velum to fill the gap between the soft palate and the posterior pharyngeal wall during velopharyngeal closure. This results in a convex configuration of the velar knee and tight velopharyngeal seal (Perry, 2011a).

Effects of Clefting on Velopharyngeal Muscles

Clefting alters the attachments of the velopharyngeal muscles. While muscular origins remain the unaffected, the insertion points are often skewed. In response to a cleft, the levator veli palatini muscle is unable to coalesce at the midline of the aponeurosis of the velum. Instead, the levator veli palatini, along with the palatopharyngeus muscle, insert into the cleft hard palate along its posterior border (Mehendale, Birch, Birkett, Sell, & Sommerlad, 2004). This leaves both muscles nonfunctional in elevating and retracting the velum. The musculus uvulae originates at the palatal aponeurosis and is commonly absent in clefts. Therefore, the musculus uvulae is altered from its beginning. [add comment that we don’t really know the nature of the MU in children/adults with clefting because it has not been studied. Histology studies on unborn fetus suggest its absence or hypoplastic but we don’t know much more than that]. A bifid or hypoplastic uvula is an initial indicator of a submucous cleft, and suggests an interruption of embryological development (Kinnebrew & McTigue, 1984; Kummer, 2013). The tensor veli palatini insertion is altered by a cleft via attachments resting along the bony cleft edges rather than the posterior border of the hard palate. This anomaly reduces its effectiveness when opening the Eustachian tube, and increases the chance of middle ear effusion and infection (Sharma & Nanda, 2009). The palatoglossus, which depresses the velum, is altered secondary to its origin being affected by the absent palatal aponeurosis. Its attachments are generally re-routed to the lateral and anterior hard palate. The superior pharyngeal constrictor and the salpingopharyngeus muscles typically go unaffected due to the lateral insertion of the muscle onto the velum (Perry, 2011a).

Palatal Elevation and VPD

Deficits in the structure and function of the above musculature can result in difficulties with appropriate palatal elevation and velopharyngeal closure needed for speech production. Individuals with cleft palate demonstrate difficulties with velopharyngeal closure pre-operatively and a significant percentage often continues to demonstrate deficiencies with velopharyngeal valving and elevation post-operatively.

Numerous methods have been proposed to assess muscle morphology and physiology of the velopharyngeal mechanism, including cadaveric studies (Huang, Lee, & Rajendran, 1998), functional anatomic studies (Dickson & Dickson, 1972) electromyography (Kuehn, Folkins, & Linville, 1988) and imaging studies of velopharyngeal closure which include radiographic, fluoroscopic, endoscopic, and magnetic resonance imaging (Simpson & Austin; 1972; Ettema & Kuehn; 1994; Moon 1987 (Ettema & Kuehn, 1994; Ettema, Kuehn, Perlman, & Alperin, 2002; Moon & Smith, 1987; Perry, Kuehn, & Sutton, 2013; Simpson & Austin, 1972). Numerous hypotheses for the underpinnings of velopharyngeal physiology have been proposed and a consensus has resulted in the assumption that velopharyngeal valving is variable across individuals and any or all of the velopharyngeal muscular may contribute at different extents to achieve appropriate velopharyngeal closure (Croft, Shprintzen, & Rakoff, 1981; Siegel-Sadewitz & Shprintzen, 1986; Skolnick et al., 1972). This variability elucidates a need for patient-specific pre-operative planning to take place when considering surgical intervention in this patient population (Shprintzen et al., 1979).

However, Dickson (1983) cites three components of normal velopharyngeal movement that typically occur across individuals which involve elevation and retraction of the velum, medial movement of the lateral pharyngeal walls, and finally lowering of the velum. These key movements must take place for appropriate speech and resonance to occur. Additionally, these components result in unique patterns of velopharyngeal closure which are necessary to consider for selection of the most appropriate surgical procedure. Elevation or height of the velum and palate has additionally been discussed in the literature as it relates to the level of velopharyngeal closure (Mason, Perry, Riski, & Fang, 2016; Riski, Serafin, Riefkohll, Georgiade, & Georgiade, 1984; Satoh, Wada, Tachimura, Sakoda, & Shiba, 1999; Satoh et al., 2004). This elevation may often correlate with recommendations for intraoperative surgical tissue placement (Carlisle, Sykes, & Singhal, 2011; Riski et al., 1984; Riski, Ruff, Georgiade, & Barwick, 1992).

Surgical Approaches to Treat Cleft Palate and VPD

Primary palatoplasty. The primary repair of a cleft palate is achieved via a palatoplasty procedure. The goal of the palatoplasty is to achieve closure of the hard and soft palate, minimize maxillary growth disturbances and dento-alveolar deformities, and create a functional anatomy for the development and production of normal speech. There are numerous surgical techniques and variations that are commonly utilized to achieve closure of a palatal cleft (Agrawal, 2009; K. S. Smith & Ugalde, 2009). Without proper closure of the cleft, patients face difficulties with communication and require subsequent surgical management.

The results of the primary palatoplasty are typically assessed by speech outcomes and maxillofacial development. When movement of the palate is sufficient to achieve closure against the posterior pharyngeal walls during speech, velopharyngeal competence is typically achieved and surgery is deemed successful. However, the literature indicates that regardless of the type of procedure used, positive outcomes are only apparent approximately 70-80% of the time (Marsh, Grames, & Holtman, 1989; Moore, Lawrence, Ptak, & Trier, 1988; Musgrave & Bremner, 1960; Phua & de Chalain, 2008; Sullivan, Marrinan, LaBrie, Rogers, & Mulliken, 2009).

Secondary surgery. Secondary management may be necessary when the velopharyngeal mechanism continues to demonstrate deficiencies in velopharyngeal closure after primary palate repair that affect speech. This is known as velopharyngeal dysfunction (VPD). Approximately 20-30% of patients following primary cleft palate repair continue to display VPD and require secondary surgery to eliminate hypernasal speech (Bicknell, McFadden, & Curran, 2002). Those with VPD are more likely than those without hypernasal speech to develop aberrant speech and compensatory errors post-surgically (Riski, 1979). VPD in individuals that have previously undergone a palatal repair is most commonly corrected with surgical management (Woo, 2012).

The most common surgical methods to treat VPD are sphincter pharyngoplasty and pharyngeal flap (Cable, Canady, Karnell, Karnell, & Malick, 2004; Sloan, 2000). Pharyngoplasties are typically performed between the ages of 2-17 when VPD is observed. The goal of surgery is to create a narrowing of the velopharyngeal space that allows velopharyngeal closure for speech and improves resonance, but avoids airway morbidity. Literature indicates similar speech outcomes across surgery types and both procedures have been associated with residual hypernasality or velopharyngeal obstruction (Sloan, 2000). An estimated 13-23% of patients will have a failed pharyngoplasty that will require an additional surgical revision (Kasten, Buchman, Stevenson, & Berger, 1997; Losken, Williams, Burstein, Malick, & Riski, 2003; Witt, Marsh, Marty-Grames, & Muntz, 1995). Secondary surgical revision is indicated when a child develops airway complications or shows no improvement in resonance (Sloan, 2000; Sommerlad et al., 1994).

Pharyngoplasties for Surgical Correction of VPD

Pharyngeal flap. The pharyngeal flap has undergone frequent study. Both inferiorly based and superiorly based pharyngeal flaps have been advocated. However, studies have indicated that the superiorly based pharyngeal flap may provide better overall outcomes (Canady, Cable, Karnell, & Karnell, 2003; De Serres et al., 1999; Whitaker, Randall, Graham, Hamilton, & Winchester, 1973). Intraoperative procedure previously utilized vertical incisions to divide the transverse fibers of the superior constrictor and elevate the posterior wall flaps. However, these incisions are reported to disrupt the continuous muscle and impair lateral pharyngeal wall movement. Thus, transverse, rather than vertical incisions, are often recommended (Kapetansky, 1975).

This surgical technique functions as a static obturator in the midline of the nasopharynx. Therefore, it creates a midline, partial obstruction with two lateral ports for breathing and nasal consonants. Lateral wall movement post-operatively is necessary for valving of the velpharyngeal port against the flap to produce oral consonants.

Sphincter pharyngoplasty. The sphincter pharyngoplasty technique uses superiorly based posterior tonsillar pillar flaps that contain the palatopharyngeus muscles. These flaps are elevated and approximated posteriorly and superiorly to insert into the pharyngeal wall. The faucial portion of the palatopharyngeus is used to increase the thickness of the posterior and lateral pharyngeal walls and consequently decrease the size of the velopharyngeal port. Early outcome reports for this surgery were reported by Hynes (1950), Orticochea (1968), Jackson and Silverton (1977), Roberts and Brown (1983) and others. More recent investigations have emphasized further modifications and the additional importance of the height of insertion for the myomuscosal sphincter flaps (Pryor et al., 2006; Riski et al., 1984).

Additional Secondary Surgical Options for Management of VPD

Palatal re-repair via palatal lengthening surgeries. There are additional reported secondary surgical options outside of a pharyngoplasty. These can include palatal re-repair via palatal lengthening surgeries and posterior wall augmentation. The use of an island flap pushback procedure has infrequently been utilized to manage VPD and has resulted in less than optimal results with velopharyngeal closure only being obtained in approximately 50% of cases and speech rarely falling within normal limits (Lewin, Heller, & Kojak, 1975; Rintala & Rantala, 1978). Recently, the Furlow palatoplasty technique has been considered a secondary option for the surgical correction of VPD (Chen, Wu, Chen, & Noordhoff, 1994; Chen, Wu, Hung, Chen, & Noordhoff, 1996). Results for this technique have been favorable, with up to 90% success rates, in patients who demonstrate small velopharyngeal gaps and those with adequate palatal tissue present (Furlow, 1995; Kirschner et al., 1999). The technique of retrodisplacement of the levator within this procedure further appears to benefit the surgical outcomes (Furlow, 1995; Sommerlad et al., 2002) and at times, this procedure has been utilized in combination with a pharyngoplasty (Gosain & Arneja, 2007).

Posterior wall augmentation. Posterior wall augmentation is typically completed via the use of autogenous implants or injections. Numerous materials have been proposed as viable to create a stationary pad or protrusion along the posterior pharyngeal wall. Materials have included cartilage (Hagerty & Hill, (1961), silicone (Blocksma, 1963), proplast (Wolford, Oelschlaeger, & Deal, 1989), and Teflon (Bluestone, Musgrave, & Crozier, 1968). However, outcome studies have indicated that these materials have not proven to be effective in the long term with success results ranging from 0-70% on average (Furlow, Williams, Eisenbach, & Bzoch, 1982; Kuehn & Van Demark, 1978; Smith & McCabe, 1977). Most recently the use of autologous fat injections has been proposed as a conservative option for the management of VPD and large scale, longitudinal outcome studies have yet to be completed (Nicolas et al., 2011).

Thus, posterior wall augmentation and palatal re-repair are less common for the remediation of VPD, as they often result in limited improvements in speech and resonance for those with greater severity of VPD post-palatoplasty. Often, patients who undergo these surgical corrections ultimately obtain a pharyngoplasty when these methods fail to produce improved speech quality. The bulk of the literature supports the use of a pharyngoplasty for the management of VPD, especially in cases where the pharyngeal depth to velar length ratio is less than favorable (D'Antonio et al., 2000).

Failures and Revision Techniques for the Pharyngeal Flap and Sphincter Pharyngoplasty

Numerous studies have assessed the failure and success rates of pharyngoplasties. Endoscopic evaluation of the failed pharyngeal flap was completed by Argamaso and colleagues (1980). Failures were primarily categorized as inadequate flap width, low-set flap insertion relative to pharyngeal wall motion, and asymmetric placement of the flap towards one side. Additionally, Crockett et al. (1988) reported a significant failure rate and discussed failure in terms of three specific areas: methods of pre-operative assessment, choice of intra-operative tissue placement, and uncontrolled wound healing. Friedman et al., (1992) found that flaps often narrow with post-operative scar contracture, thus increasing the overall velopharyngeal port size. However, the amount of scar contracture over time was not documented. This leaves little insight for pre-emptive intraoperative modifications to prevent negative outcomes associated with scar contracture.

Revision of failed pharyngeal flaps was completed by Hirshowtiz and Bar-David (1976). Within this study, flaps were revised via elevation and rotation and then insertion into the superior surface of the soft palate. Friedman et al., (1992) reported on revisions that utilized superiorly based flaps that were elevated laterally from the sides of the failed flaps. In these cases, elevation of the pharyngeal flap led to improved nasalance post-revision. Additionally, lining of the flap has been advocated to prevent post-operative narrowing (Isshiki & Morimoto, 1975; Johns, Cannito, Rohrich, & Tebbetts, 1994; Owsley Jr, Lawson, Miller, & Blackfield, 1966). This is a common feature of modern pharyngeal flap operations.

Similar results have been noted in failures and revisions to sphincter pharyngoplasties. Riski et al. (1992) observed the primary cause of failed pharyngoplasty was insertion of the sphincter flaps below the point of attempted velopharyngeal contact. To reduce failure rate, Riski et al. (1984) demonstrated the use of pre-operative lateral radiographs during sustained phonation to determine the level of attempted velopharyngeal closure relative to the first cervical vertebra. The first cervical vertebra was used to provide an intra-operative landmark so that the pharyngoplasty is inset above this palpable landmark. Carlisle et al. (2011) discusses routinely placing the myomucosal flaps as high in the nasopharynx as feasibly possible, oftentimes resecting a portion of adenoid tissue. Others have also advised elevating the height of insertion as high as possible (Jackson & Silverton, 1977; Roberts & Brown, 1983) in order to increase success rate. Although clinically this approach is feasible, it provides no insight into what constitutes "high enough" for proper velopharyngeal function. Furthermore, it provides no quantitative method to guide surgical planning and determine prognosis.

Riski et al. (1984), in a report on their institutions 15-year experience, suggested a rationale for tailoring the height of flap insertion. The height of attempted velopharyngeal contact was identified relative to the anterior tubercle of the first cervical vertebrae. Palpation of this landmark intraoperatively assists in identifying the point that the flaps ideally should be inserted based on the predetermined height of velopharyngeal closure. Studies, however, have failed to quantify the optimal level of insertion and demonstrate a clear intra-operative approach for ensuring proper placement. In addition, due to unknown factors such as mobility of the pharyngoplasty post-surgically and the effects of scaring/growth on outcome, optimal insertion height may be further under-assessed. If the point of attachment to the pharyngeal wall changes, misalignment of the palate and the pharynx may tether the sphincter flaps downward (Friedman et al., 1992). Huang and colleagues (1998) expands on this, asserting that the level of flap inset is significant, as inset at the level of the uvula has the greatest risk of causing obstruction, whereas a higher inset at the level of attempted velopharyngeal closure provides the best opportunity for achieving velopharyngeal competence while avoiding airway morbidity.

Although studies have emphasized the importance of placing a pharyngoplasty at or above the level of velopharyngeal closure (Carlisle et al., 2011; Riski et al., 1992; Witt et al., 1995), clinical methods tend to be less prescriptive indicating placement should be "as high as possible." Thus far, no studies have quantified the optimal level of insertion of pharyngoplasties relative to any bony or palpable intraoperative landmarks, taking into account how post-surgical tissue changes. Satoh et al. (1999) proposed a coordinate system based on differing celphalometric landmarks and the palatal plane to measure the variation in the vertical relationship between the palatal plane and level of velopharyngeal contact (Satoh et al., 1999). A coordinate system is useful in research, however, may not be clinically feasible. Furthermore, there is little agreement on the precise intra-operative approach for ensuring proper placement.

In contrast, palpation of C1 is reported to serve as an intraoperative landmark to assist in identifying the optimal placement for the pharyngoplasty based on the predetermined height of velopharyngeal closure (Riski et al., 1992). Reports by Mason et al. (2016) suggest that utilizing the measure of the vertical distance between the palatal plane and C1 preoperatively may be of clinical interest in patients who undergo secondary speech surgeries due to the change in the vertical distance between these landmarks as the child ages. Data suggest that as a child ages, specifically between the ages of 4-9, an increase in the vertical distance is observed between the anterior tubercle of C1 and the palatal plane (Mason et al., 2016). This may infer that for children undergoing secondary surgical treatment for VPD, the pharyngoplasty may need to be placed higher in the nasopharynx relative to C1. Secondarily, Mason and colleagues (2016) reported that C1 was noted to consistently reside below the level of velopharyngeal closure. Thus, it can be inferred that placement of the sphincter flaps or pharyngeal flap at C1 would result in a pharyngoplasty positioned below the level of effective VP closure. Poor surgical outcomes, secondary to placement of pharyngoplasty below the point of velopharyngeal contact, could be further exacerbated if surgical placement at C1 occurs after the age of 10, due to a greater distance between C1 and the palatal plane being present (Mason et al., 2016). Additionally, it is still unclear how far above C1 and the level of velopharyngeal closure the pharyngoplasty should be placed in order to account for post-surgical tissue change.

Thus, the above factors may play a role in the failure rate and be associated with the low-set pharyngoplasties that post-operative assessment tends to reveal. Questions arise regarding how much movement is observed post-operatively relative to the intraoperative tissue placement, how this movement may affect speech outcomes, and how intra-operative methods can preventatively control for this change that is observed.

Summative Cause Surgical Failures and Revisions

While numerous studies have outlined the suspected causes of surgical failure, little is known regarding the gold standard for intraoperative procedure and post-operative tissue change. This is due, in part, to a lack of quantifiable intra-operative measures.

It is well documented that pharyngoplasties alter the relationship between the posterior pharyngeal wall and the velum using a pharyngeal flap to connect the velum to the posterior pharyngeal wall or by creating a sphincter to narrow the overall size of the velopharyngeal port. Studies have emphasized the importance of placement of the pharyngoplasty as it relates to speech outcome (Carlisle et al., 2011; Riski et al., 1984; Witt et al., 1995). The first cervical vertebra (C1) or the level of velopharyngeal closure have been recommended as landmarks for identifying placement of the pharyngoplasty prior to and during surgery in order to ensure the pharyngoplasty is at an optimal level for normal resonance postsurgically (Carlisle et al., 2011; Riski et al., 1984).

Marsh (2009) reports on limited consensus regarding the precise surgical method or timing of outcome assessment following VPD management. Success is broadly defined as a combination of the elimination of the symptomatic manifestations of VPD in conjunction with the maintenance of a patent nasopharyngeal airway. Similar to results reported by Peat et al. (1994), numerous studies indicate that more precise methods of surgical intervention are needed which must take into account pre-operative analyses. Additionally, vascular bases of current pharyngoplasty methods are questionable and variability of scar tissue formation impacts precision in the area of the pharyngoplasties. Notably, only millimeters of inappropriate change, whether from contracture of the flap tissue or inset of the pharyngoplasty, can dramatically affect resonance and speech outcomes (Peat et al., 1994).

Necessity of Patient-Specific Pre-operative Measures for Surgical Planning

Shprintzen and colleagues (1979) evaluated the effectiveness of differing procedures for varying flap width using pre-operative imaging methods (nasendoscopy and videofluoroscopy). Within this study of 120 patients, the sample was divided in half and 60 patients were randomly assigned to a surgeon who selected a pharyngoplasty type based on experience with a specific procedure. The remaining patients in the study were assigned a surgical procedure based on patient specific, pre-operative findings regarding the velopharyngeal mechanism and then assigned to a surgeon for operation. Results obtained when the surgical procedure was based on a patient's pre-operative anatomy were more favorable than those that were completed based on surgeon skill and preference. This substantiates the need for detailed pre-operative, and patient-specific, surgical planning.

Imaging Analyses and Development of MRI

Pre-operative surgical recommendations are typically made from perceptual judgments of resonance and imaging methods such as cephalometrics, videofluoroscopy and/or nasendoscopy. Taking these measures a step further, magnetic resonance imaging (MRI) provides the potential for improved visualization of structures within the oro- and naso-cavities as well as posterior pharynx.

Magnetic resonance imaging is the only imaging modality that allows visualization of the internal musculature *in vivo*. Studies have examined the velar musculature in adults with normal anatomy (Bae, Kuehn, Sutton, Conway, & Perry, 2011; Ettema et al., 2002; Perry, 2011b; Perry et al., 2013; Tian & Redett, 2009), adults with cleft palate anatomy (Ha, Kuehn, Cohen, & Alperin, 2007), children with normal and cleft palate anatomy (Kollara & Perry, 2014; Tian et al., 2010), and infants with normal and cleft palate anatomy (Kuehn, Ettema, Goldwasser, & Barkmeier, 2004; Perry, 2011b). These MRI studies demonstrate the value of using MRI and the potential clinical utility to improve post-surgical speech outcomes.

Rationale for Continued and Advanced MRI Investigations

Literature has demonstrated that imaging assessments are essential in the pre-operative evaluation process and MRI allows for new investigation and significant insight for examining the extent of migration that tissue undergoes from the time immediately post-operatively through the post-operative follow-up evaluations. It is unknown the extent to which this migration occurs and how this migration effects speech outcomes. Thus far, no studies have applied the use of MRI imaging methods immediately postoperatively to examine initial placement and movement of the pharyngoplasty in the cleft palate population. This study will incorporate the use of MRI in the analysis of post-operative anatomical changes. The innovative significance of this research will provide direct visualization of the velopharyngeal muscle anatomy *in vivo* in individuals with VPD allowing for the direct comparison of pre-operative measures and discover further details of the velopharyngeal musculature. This is the first study to assess the changes in craniometric measures pre- and post-operatively as well as continued changes that occur with time. Moreover, this study will provide insight into the impact of anatomical variations of secondary surgical outcomes among this population.

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CHAPTER 3

STUDY I

Age Related Changes between the Level of Velopharyngeal Closure and the Cervical Spine[1]

ABSTRACT

The primary focus of this study was to assess age related changes in the vertical distance of the estimated level of velopharyngeal closure in relation to a prominent landmark of the cervical spine: the anterior tubercle of cervical vertebrae one (C1). Midsagittal anatomical magnetic resonance images (MRI) were examined across 51 participants with normal head and neck anatomy between 4 and 17 years of age. Results indicate that age is a strong predictor (p = 0.002) of the vertical distance between the level of velopharyngeal closure relative to C1. Specifically, as age increases, the vertical distance between the palatal plane and C1 becomes greater resulting in the level of velopharyngeal closure being located higher above C1 (range 4.88mm to 10.55mm). Results of this study provide insights into the clinical usefulness of using C1 as a surgical landmark for placement of pharyngoplasties in children with repaired cleft palate and persistent hypernasal speech. Clinical implications and future directions are discussed.

INTRODUCTION

The cranial and velopharyngeal soft tissue structures develop and change across the age span (Subtelny, 1957). Age related changes are evident in the horizontal and vertical dimensions of the vocal tract and contribute to normal velopharyngeal anatomy and function (Perry JL, Kollara, L, Schenck G, Fang X, Kuehn DP, Sutton, BP, in press). Between 4-17 years of age, vertical growth of the vocal tract causes changes in the angle of the posterior pharyngeal wall,

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[1] Mason, K. N., Perry, J. L., Riski, J. E., & Fang, X. (2016). Age related changes between the level of velopharyngeal closure and the cervical spine. *Journal of Craniofacial Surgery*, *27*(2), 498.

moving from an obtuse angle to an approximately right angle (Kent & Vorperian, 1995). Ursi and colleagues (1993) found that facial, maxillary, and mandibular growth showed no sexual dimorphism prior to puberty. Perry et al (2014) demonstrated non-significant gender effects for cranial, velopharyngeal, and levator muscle measures prior to puberty with notable growth variations occurring post-puberty. (13-19 years of age) Perry et al (2014), in agreement with other studies (Satoh, Wada, Tachimura, Sakoda, & Shiba, 1999; Satoh et al., 2004; Wu & Epker, 1990; Yoshida, Stella, Ghali, & Epker, 1992), further demonstrated velopharyngeal closure at or along the palatal plane. Thus, the level of velopharyngeal closure is closely associated with the palatal plane in the child population (Satoh et al., 1999).

Velopharyngeal dysfunction (VPD) occurs in approximately 5-38% of children with repaired cleft palate (Witt & D'Antonio, 1993). A pharyngoplasty is typically used for surgical correction of VPD. Pharyngoplasties alter the relationship between the posterior pharyngeal wall and the velum. The success of speech outcomes corresponds to the patient’s preoperative craniofacial morphology (El-Kassaby, Abdelrahman, & Abbass, 2013; Heliövaara, Leikola, & Hukki, 2013). Preoperative morphology has primarily been assessed in the orthognathic and dental literature and focused on anterior craniofacial structures (Heliövaara et al., 2013). Craniofacial soft tissue structures and their functions have further been a focus of recent studies (Cheng et al., 2006; Gart & Gosain, 2014; Huang, Lee, & Rajendran, 1998; Perry, 2011; Trier, 1983). Specifics of the craniofacial structures and the upper cervical spine along with changes across the age span as they relate to surgical outcomes warrant further analysis. Specifically, it is not well understood how growth and angulation changes in the pharyngeal cavity effect the decisions of optimal surgical placement.

An estimated 13-23% of patients will have a failed pharyngoplasty that requires a surgical revision (Kasten, Buchman, Stevenson, & Berger, 1997; Losken, Williams, Burstein, Malick, & Riski, 2003; Witt, Marsh, Marty-Grames, & Muntz, 1995). Riski et al. (1992) observed the primary cause of failed pharyngoplasty was insertion of the flap below the point of optimal velopharyngeal closure. Studies have emphasized the importance of placement of the pharyngoplasty as it relates to speech outcome (Carlisle, Sykes, & Singhal, 2011; Riski, Serafin, Riefkohll, Georgiade, & Georgiade, 1984; Witt et al., 1995), suggesting placement at or above the level of velopharyngeal closure (Carlisle et al., 2011; Riski et al., 1992; Witt et al., 1995). However, clinical methods tend to be less prescriptive indicating placement should be "as high as possible." The first cervical vertebra (C1) or the level of velopharyngeal closure have been recommended as landmarks for identifying placement of the pharyngoplasty prior to and during surgery in order to ensure the pharyngoplasty is at an optimal level for normal resonance postsurgically. To our knowledge, no studies have quantified the optimal level of insertion of pharyngoplasties relative to any bony or palpable intraoperative landmarks. Given the range in age of surgery for pharyngoplasties can be extensive (2-17 years of age), further information is needed to understand how changes in the pharynx due to growth effect the relationship of C1 to level of velopharyngeal closure. It is expected that as the vocal tract lengthens and changes in the vertical configuration occur across the age span, the relationship between C1 and palatal plane will likely be altered. Research is needed to understand the relationship of palatal plane in normal anatomy relative to age related changes in the cervical spine to determine the need for future research with clinical populations.

The purpose of this study is to determine if C1 remains at the same location relative to the level of velopharyngeal closure (using the palatal plane as a reference line) across a selected age span. Consistent with vocal tract literature demonstrating cervical growth patterns across the age span (Satoh, Wada, Tachimura, & Shiba, 2002; H. K. Vorperian et al., 2005; Vorperian, Houri K Wang, Shubing Chung, Moo K Schimek, E Michael Durtschi, Reid B Kent, Ray D Ziegert, Andrew J Gentry, Lindell R, 2009), it is expected that the relationship between C1 and the palatal plane will show similar changes with age. Specifically, we hypothesize that the vertical distance between C1 and the level of velopharyngeal closure will increase with age. This study seeks to examine age related changes and the usefulness of the palatal plane in relation to the cervical spine for evaluating the level of velopharyngeal closure.

METHODS

Participants

In accordance with the University Medical Center Institutional Review Board (UMIRB) 51 participants were recruited to participate in the study. Male and female participants (26 male, 25 female) were included between the ages of 4 and 17 years (mean, 9.59; SD 4.383). Participants were stratified across age groups including 15 child participants (4-6 years of age; mean 4.87 ± 0.83), 17 prepubescent participants (7-9 years of age; mean 8.18 ± 0.883), 6 peri-pubescent participants (10-14 years of age; mean 11.67 ± 1.86) and 13 adolescent/post-pubescent participants (14-17 years of age; mean 15.92 ± 0.64). Age groups were selected based on the stages of development from childhood through adolescence and notable changes that are known to occur with the craniofacial and skeletal development during puberty (Vorperian et al., 2011). A similar number of boys and girls were recruited within each age category. Prior studies have demonstrated no gender effects in craniometric and velopharyngeal measures prior to puberty (Kollara & Perry, 2014; Perry JL, Kollara, L, Schenck G, Fang X, Kuehn DP, Sutton, BP, in press). Therefore, we do not expect the majority of data from the present study to be influenced by gender. Participants reported no history of craniofacial, cervical spine abnormalities, neurological, swallowing, or musculoskeletal disorders. No syndromic conditions were reported. Oral exam and a 7-point perceptual rating scale confirmed normal oral anatomy and normal resonance. Midsagittal MR images were examined to ensure exclusion of participants with cervical spine abnormalities.

Magnetic Resonance Imaging (MRI)

Procedures for MRI scanning have been previously described (Perry, 2011). Participants were scanned using a Siemens 3 Tesla Trio (Erlangen, Germany) and a 12-channel Siemens Trio head coil. During the 5-minute scan, participants were instructed to breathe through their nose with their mouth closed. Previous studies have found that supine imaging data can be translated to an upright activity such as speech (Bae, Kuehn, Sutton, Conway, & Perry, 2011; Kollara & Perry, 2014; Perry, 2011). Thus, imaging was obtained while in the supine position allowing the velum to rest in a relaxed and lowered position.

A Velcro-fastened elastic strap was placed around the participant's head, passing above the glabella and fastened to the head coil to reduce head motion. A high-resolution, T2-weighted turbo-spin-echo (TSE) three-dimensional anatomical scan called SPACE (Sampling Perfection with Application optimized Contrasts using different flip angle Evolution) was used to acquire a large field of view covering the oropharyngeal anatomy (25.6 × 19.2 × 15.5 cm) with 0.8 mm in plane isotropic resolution with an acquisition time of slightly less than 5 minutes (4:52). Echo time (TE) was 268 milliseconds, and repetition time (TR) was 2.5 seconds.

Image Analysis

MRI data were transferred into Amira 5.6 Visualization and Volume Modeling software (Mercury Company Systems Inc, Chelmsford, MA), which has a built-in native Digital Imaging and Communications in Medicine (DICOM) support program. This software ensures the anatomical geometry (e.g., aspect ratio, scaling dimension, and image resolution) is maintained when importing images into the program. The midsagittal plane was determined by identifying the section plane that most clearly depicts the complete nasal septum, genu of the corpus callosum, and outline of the fourth ventricle. Quantitative measures of the cranial base angle, the line of the palatal plane estimating velopharyngeal contact to the posterior pharyngeal wall, vertical distance of estimated velopharyngeal contact to C1, pharyngeal depth, and velar length were obtained from the midsagittal MRI plane (Figure A2). Cranial base angle and the velar/pharyngeal depth to length ratios were then computed. Means and standard deviations are displayed in Table A2. Descriptions of these measures obtained at rest, similar to Tian et al. (2010), are further enumerated below.

a) Cranial Base Angle: Angle created by the intersection of the nasion-sella line and sella-basion line.

b) Velar Length: Curvilinear distance between the posterior border of the hard palate (PNS) and center of the uvula at rest.

c) Pharyngeal Depth: Distance from velar knee at rest to the posterior pharyngeal wall drawn parallel to palatal plane.

d) Nasopharyngeal Depth (PNS to PPW): Distance between the posterior border of the hard palate (PNS) and the posterior pharyngeal wall (PPW).

e) <u>Palatal Plane Reference Line</u>: Line drawn through the body of the hard palate and extending posteriorly through the posterior pharyngeal wall.

f) <u>Vertical Distance from Palatal Plane Reference Line Relative to C1</u>: Distance from the anterior tubercle of C1 vertically (coursing parallel to the pharyngeal wall) to the palatal plane reference line (Figure A1).

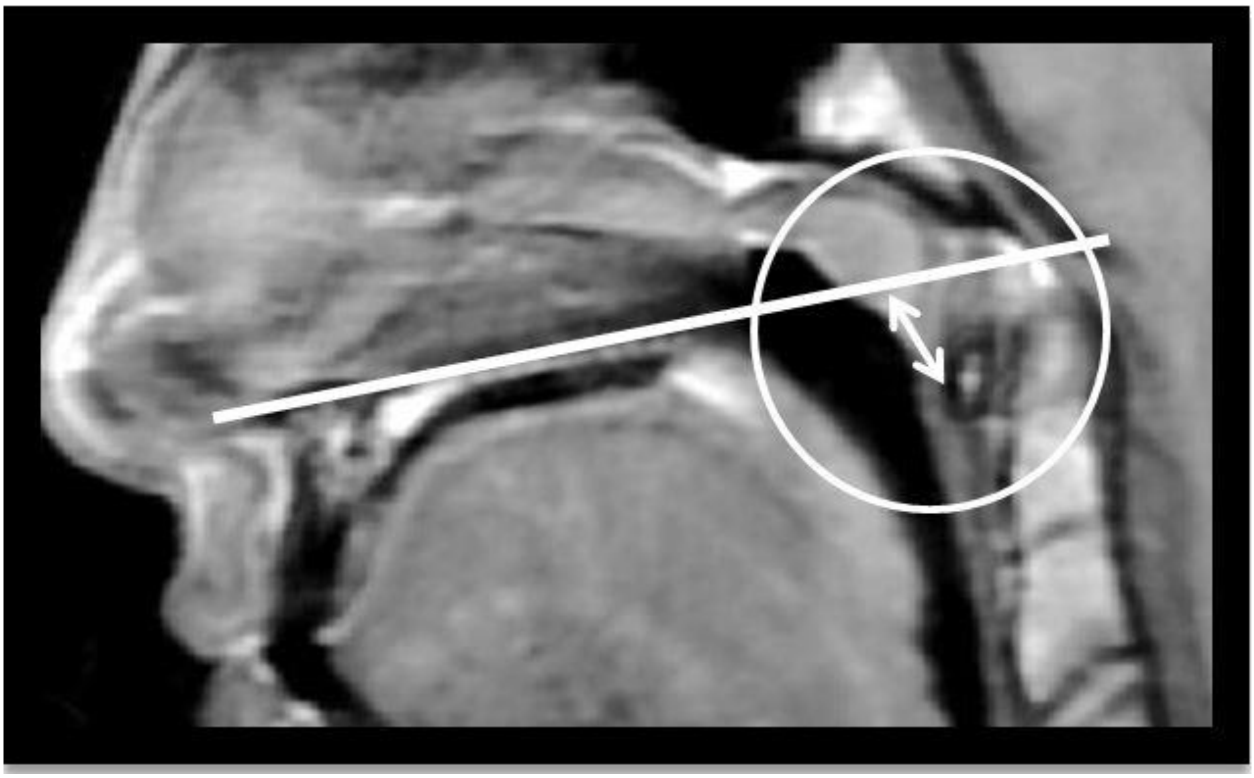

Figure A1. Reference line of the palatal plane and vertical distance between the anterior tubercle of C1 and the level of velopharyngeal closure.

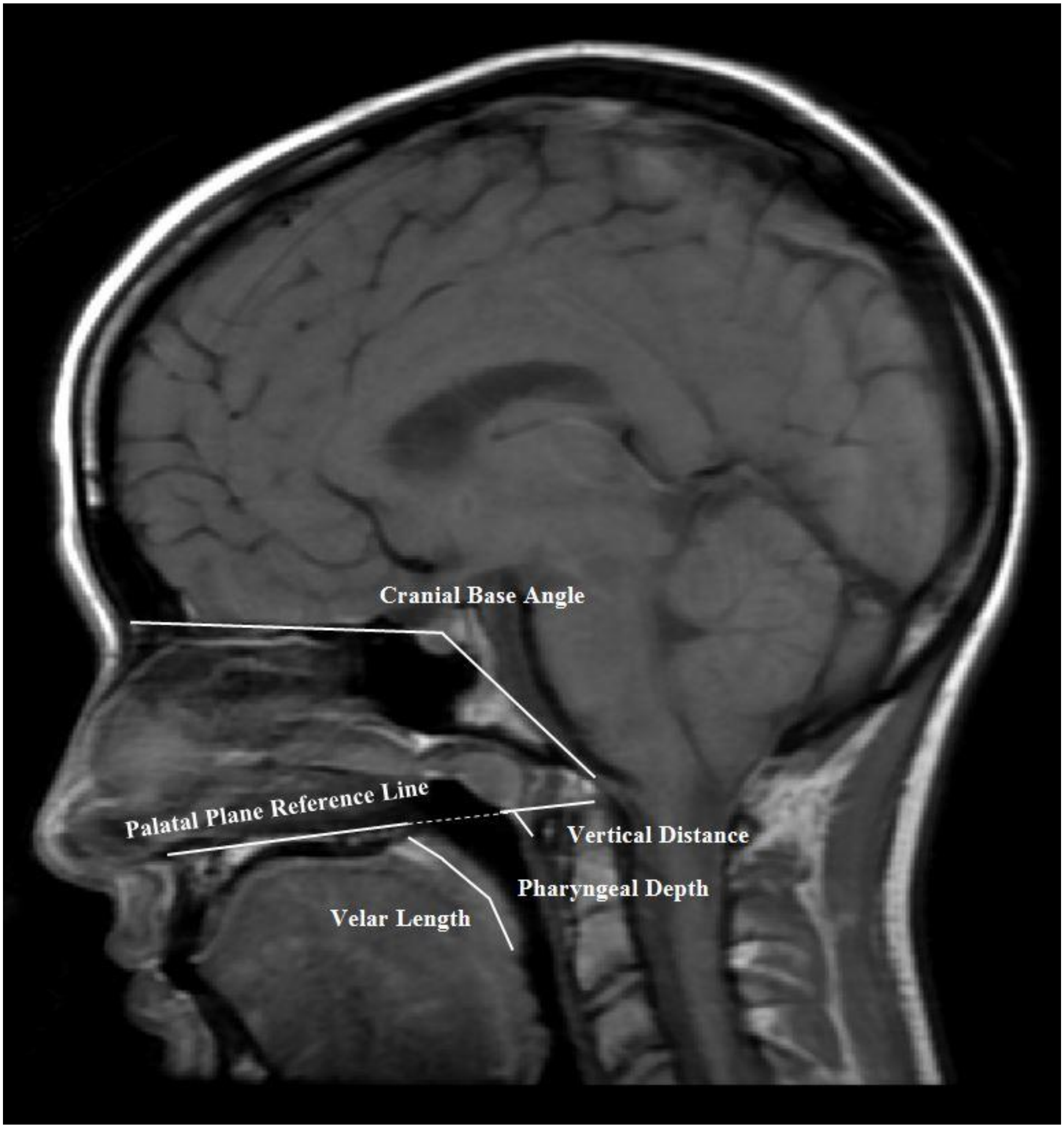

Figure A2. Sample Measures Obtained.

The Pearson product moment correlation (α = 0.05) was used to establish interrater and intrarater reliability measures. Reliability measurements were completed on 10 randomly selected mid-sagittal MRI slices by the primary and secondary raters 3 weeks after the first measures were obtained. Both raters have prior experience in measuring the areas and structures in this study. The interrater and intrarater reliability ranged from r = .98 to r =.99.

Statistics

Statistical analyses were conducted with SPSS 20.0 (IBM Corp., Armonk, NY) on 51 children to determine age variations and interactions among craniometric variables including vertical distance of the palatal plane relative to C1, pharyngeal depth, velar length, and cranial base angle. A two sample t-test on gender and cranial measures (the vertical distance of the level of VP closure to C1) were used to assess the homogeneity of our sample to determine if differences were present secondary to sexual dimorphism within each age group.

An analysis of covariance (ANCOVA) using the general linear model procedure in SPSS (IBM Corp.) was used to determine the interactions between age and vertical distance of the estimated level of velopharyngeal closure to C1 using the covariate of race to control for the effects of racial difference on cranial measures.

Linear regression analysis was performed to determine whether age could be used to predict the vertical distance of the estimated level of velopharyngeal closure relative to C1. It was hypothesized that age would affect the vertical distance of the palatal plane/estimated level of velopharyngeal closure relative to C1. Cranial base angle was found to be consistent across all measures, thus it was not included in the statistical analyses or regression model.

RESULTS

Two sample t-tests were used to assess if gender differences secondary to pubertal growth effects were present within groups. No statistically significant differences were seen related to sexual dimorphism across all groups (Table A1). This indicates that for the measures used in the present study, there do not appear to be gender differences within each group.

Table A1.

No Significant Differences in PP to C1 between Male vs Female within Age Groups

Two Sample T-Test			
	Mean Male	Mean Female	Significance
Child Age 4-6	-7.21 ± 1.04	-6.63 ± 1.28	0.352
Prepubescent Age 7-9	-8.01 ± 1.25	-7.49 ± 1.23	0.402
Peripubescent Age 10-14	-9.725 ± 0.71	-8.365 ± 0.90	0.142
Postpubescent Age 15-17	-9.025 ± 1.61	-7.649 ± 2.06	0.213

*α = 0.05

Means and standard deviations are reported for craniometric measures on all participants (Table A2). Cranial base angle was found to be consistent across all participants with little variability between age and gender groups. Pharyngeal depth increased across the age span for all participants with the largest increase noted from the pre- to peri-pubescent group, followed closely by the adolescent/post-pubescent group. Velar length was noted to increase, with the greatest difference in means noted between the peri-pubescent and post-pubescent groups. Values within our sample were consistent with previous literature (Subtelny, 1957). The variability observed in the vertical distance between the level of VP closure and C1 was demonstrated by a large spread across measures in the post-pubescent age group (4.91 to 10.55 mm). This is in contrast to the child and pre-pubescent groups which had smaller spreads (4.88 to 9.51 mm and 5.87 to 9.69 mm, respectively).

Table A2.

Means and standard deviations for measures across age groups (in mm)

Age Group	*Cranial Base Angle*	*Pharyngeal Depth*	*Velar Length*	*PNS to PPW*	*Vertical Distance between PP and C1*
Child Ages 4-6	130.63º ± 3.35	7.88 ± 1.10	24.39 ± 1.81	18.69 ± 3.43	6.94 ± 1.15
Prepubescent Ages 7-9	130.66º ± 1.82	8.27 ± 1.22	27.30 ± 2.47	19.75 ± 3.18	7.77 ± 1.23
Peripubescent Ages 10-14	128.35º ± 4.33	10.07 ± 2.47	28.21 ± 0.99	19.92 ± 2.50	8.82 ± 1.04
Postpubescent Ages 15-17	130.20º ± 2.53	11.02 ± 1.87	32.17 ± 3.53	24.95 ± 4.06	8.28 ± 1.93
Overall Mean Mean age 9.59	130.26º ± 2.86	9.07 ± 2.00	27.79 ± 3.81	20.78 ± 4.17	7.78 ± 1.51

Regression analysis was performed to determine if age was a predictor of the vertical distance from the level of VP closure to C1. Age, when treated as a continuous variable, was found to be statistically significant ($p = 0.002$). A moderate correlation ($R = 0.402$) was observed across all participant measures of vertical distance (Figure A3). In such, C1 becomes farther below the estimated level of velopharyngeal closure with an increase in age (Figure A4).

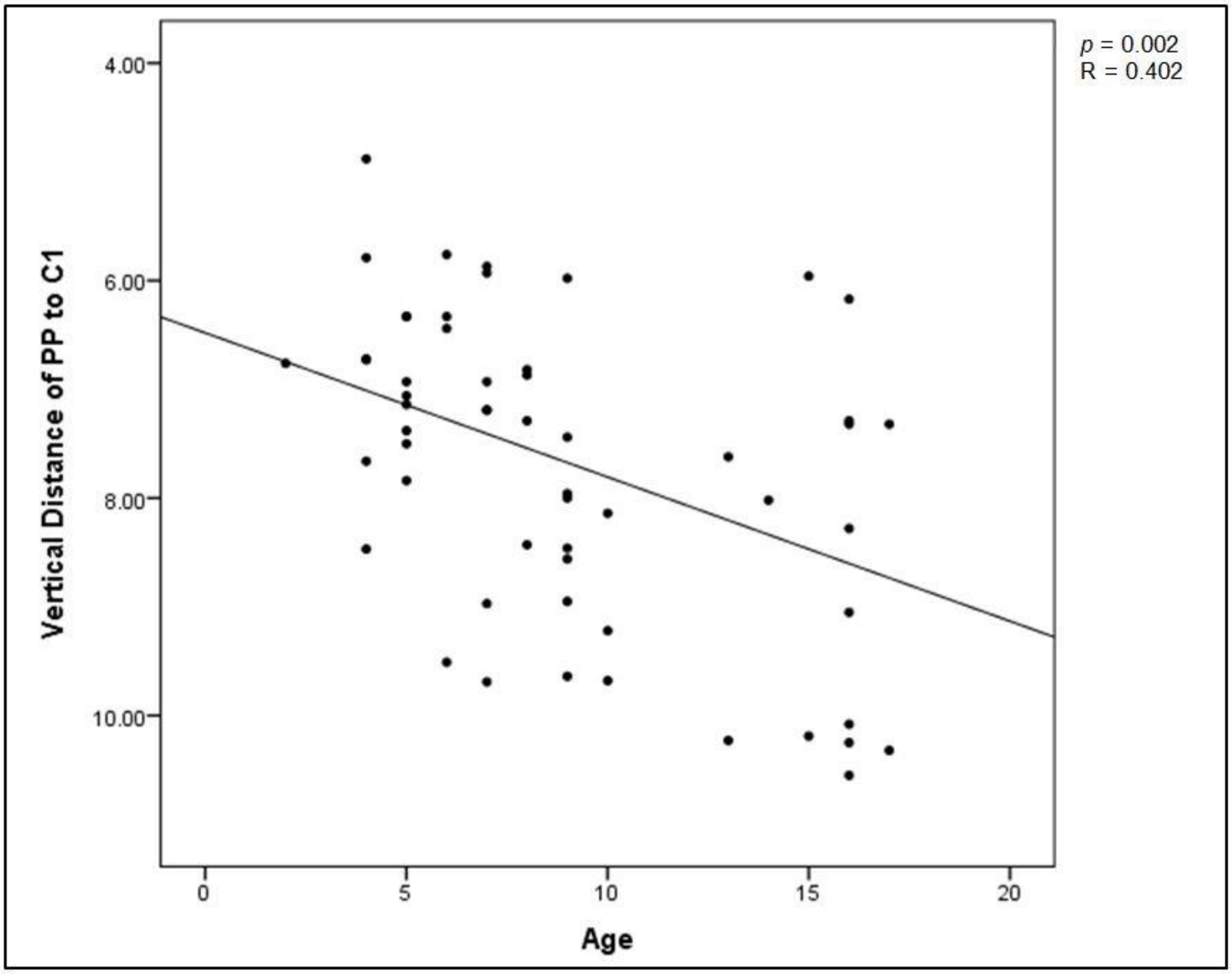

Figure A3. Regression of age (in years) to vertical distance (in mm) between level of VP closure and C1.

Figure A4. Example of vertical distance between C1 and palatal plane in a 4 year old female compared to a 17 year old female.

Greater variability in the vertical distance of palatal plane to C1 was observed in the peri-pubescent and adolescent group compared to the child and pre-pubescent age groups (Figure A5). Specifically, after age 10, the downward trend becomes less apparent due to the variability in vertical distance. This indicates that between the ages of 4-9, vertical distance between C1 and the level of velopharyngeal closure steadily increases. Following age 10, variability in the vertical distance between participants was observed (indicating differences in the peri-pubertal growth spurts) and greater vertical distances were measured. Thus, age is a stronger predictor of the vertical distance for the child group (ages 4-9). During the peri-pubertal and post-pubertal stages it is likely that other pubertal growth factors may begin to play a larger role.

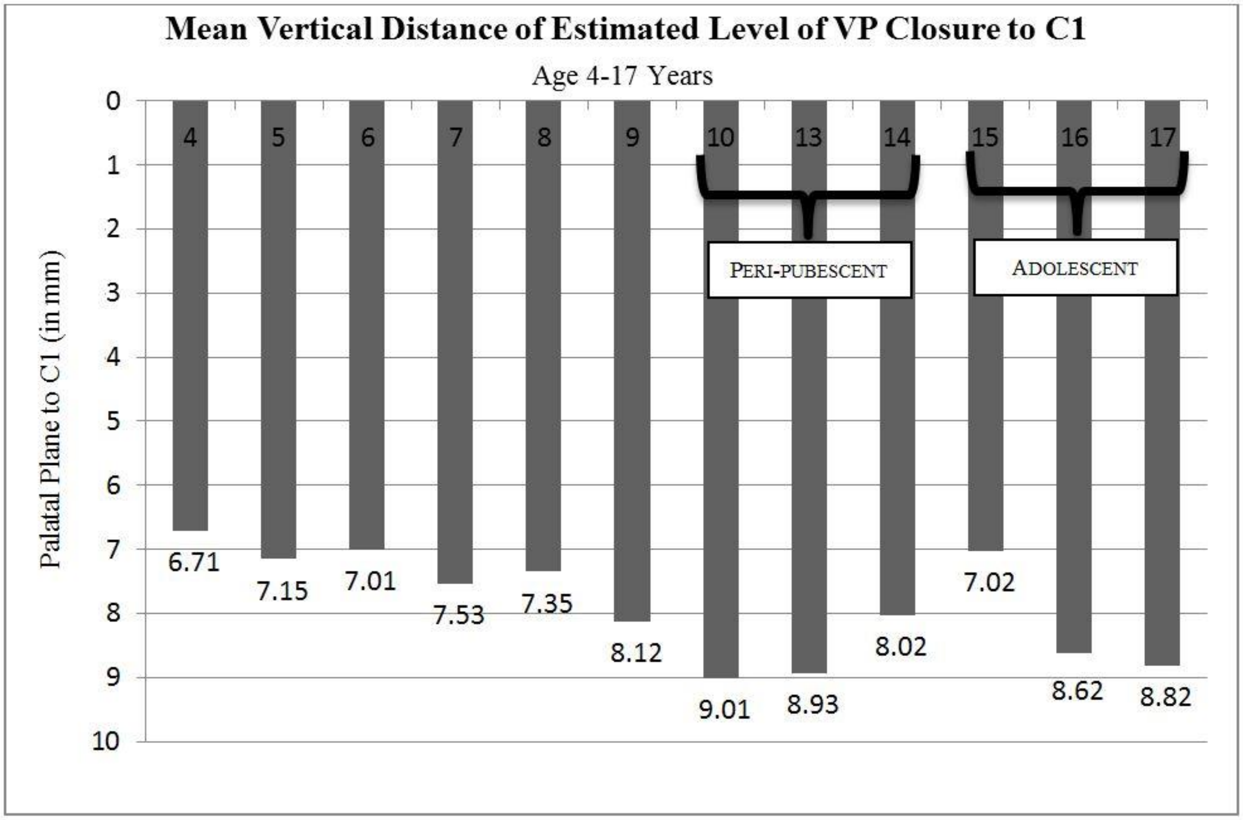

Figure A5. Mean vertical distance of palatal plane to C1 across age span.

An analysis of covariance (ANCOVA) was completed across age groups (child, prepubescent, peri-pubescent, and adolescent) with race treated as a covariate to determine if differences in the mean vertical distance between the level of closure and C1 for each group were present between age groups. Results were statistically significant at $\alpha = 0.05$ ($p = 0.029$). A Bonferoni post-hoc test revealed the greatest difference occurred between the child and adolescent groups.

DISCUSSION

Historically, the palatal plane has been defined as the measure of the anterior nasal spine (ANS) to the posterior nasal spine (PNS) (Courtney, Harkness, & Herbison, 1996; Satoh et al., 1999; Satoh et al., 2002; Wada, Satoh, Tachimura, & Tatsuta, 1997). These structures create easily recognizable landmarks. However, consistent with past studies (Durtschi, Chung, Gentry, Chung, & Vorperian, 2009; Harris, Kowalski, LeVasseur, Nasjleti, & Walker, 1977; Mooney & Siegel, 1986), significant variability was seen in the location and prominence of the ANS across the images in the present study. This noted variability included a higher curving or more superiorly placed ANS in some individuals. This influences the line of reference drawn through to the PNS. Further, it has been reported that the ANS can be significantly angled both superiorly and inferiorly in the cleft lip and palate population (Molsted & Dahl, 1990), can vary by race(Mooney & Siegel, 1986), and patients with cleft palate do not display a prominent PNS (Bishara, 1973). The use of the ptergomaxillary fissure is suggested to estimate the location of the PNS in the cleft population (Bishara, 1973; Graber, 1949). Frequently, when using the ANS-PNS line for participants within our sample, the body of the palate was disregarded and the reference line did not course directly through the body of the palate with differing variations of the ANS. Thus, this study used the body of the palate through the PNS (directly below the ptergomaxillary fissure in normal participants) to determine the level of the palatal plane as an estimator of velopharyngeal closure or contact with the PPW. This allowed for the creation of a consistent plane of reference for which to measure an estimated level of velopharyngeal closure (against the posterior pharyngeal wall). Past literature has demonstrated velopharyngeal closure occurs along this palatal plane reference line (Satoh et al., 2004; Yoshida et al., 1992), however, it is expected that changes in velar contact along the posterior pharyngeal wall demonstrate a pubertal shift that is beyond the age range used in the present study. In such, velar height variations that have been demonstrated in adult populations (Kuehn, Folkins, & Cutting, 1982;

McKerns & Bzoch, 1970) are likely not evident in the age ranges used in the present study. This is consistent with prior studies examining velar variations across the age span.

Similar to Ursi et al. (1993), cranial base angle values in the present study were consistent across all age groups, with minimal variation between males and females. Despite known increases in head size for boys and girls across the age span, cranial base angle remains consistent across age and gender for the age range used in the present study. Pharyngeal depth and velar length showed a trend to increase with age. These findings are similar to those found by Subtelny (1957) and parallel the consistent increase found in studies of velar length and nasopharyngeal depth (Subtelny, 1957; Tian & Redett, 2009; H. K. Vorperian et al., 2005). Within each age group, no significant differences in cranial measures were noted. Due to the majority of our data being from pre-pubertal participants, these results were expected. Non-significant gender differences are consistent with findings from Perry et al. (in press) in which sexual dimorphism of cranial and velopharyngeal variables were primarily evident in post-pubertal age groups. However, variability in the vertical distance between the palatal plane and C1 was noted across age groups and most significantly observed in the peri- and post-pubescent age groups. This variability is likely due to changes in the vocal tract descent and angulation (Perry JL, Kollara, L, Schenck G, Fang X, Kuehn DP, Sutton, BP, in press).

Previous studies have assessed height of insertion of pharyngoplasties relative to C1 (Riski et al., 1984; Riski et al., 1992; Witt, D'Antonio, Zimmerman, & Marsh, 1994). Riski et al. (1984) demonstrated that the insertion height of the pharyngoplasty appeared to be a critical factor in surgical success. However, quantification for the ideal height of insertion has not been reported. To our knowledge, no studies have examined how this palpable bony landmark (C1) relative to the palatal plane and level of velopharyngeal closure may change with age. The anterior tubercle of C1 is commonly palpated and used as an identifying landmark for the placement of tissue during surgical insertion of a pharyngoplasty (Riski et al., 1992). Our study sought to assess if age related changes affected the vertical distance from the level of velopharyngeal closure to C1. Our results indicate age is significantly correlated to the vertical distance between the palatal plane (point of velopharyngeal contact against the posterior pharyngeal wall) and the anterior tubercle of C1 ($p = 0.002$, $\alpha = 0.05$).

Statistically significant correlations were further present for age as a predictor in the level of velopharyngeal closure relative to the vertical distance above C1. As age increases, the level of velopharyngeal closure is higher above C1. This is likely due to the accelerated growth of the vertebral column (Vorperian, Houri K Wang, Shubing Chung, Moo K Schimek, E Michael Durtschi, Reid B Kent, Ray D Ziegert, Andrew J Gentry, Lindell R, 2009). The anterior tubercle of C1 was consistently below the level of velopharyngeal closure in all participants. Quantitatively, a range of 4.88mm to 10.55mm was seen in the vertical distance between C1 and palatal plane across the age span of 4-17 years. Table A2 displays the mean vertical distance between C1 and palatal plane within each age group. Our data suggest that age affects the vertical distance between C1 and the level of velopharyngeal closure among the child population. Contrary to previous tracings of craniofacial growth (Coccaro, Pruzansky, & Subtelny, 1967), which illustrate smaller distances between C1 and the palatal plane as the child ages, data from this study demonstrate an increased distance between the level of velopharyngeal closure and the palatal plane as the child ages.

This study highlights anatomical landmarks in a normal population that can be utilized as a reference for a disordered population. Previous studies have primarily focused on outcomes for specific speech surgeries and techniques to improve their success with little focus on a patient's preoperative bony anatomy as it relates to the structural development and function of the velopharyngeal mechanism (Sloan, 2000; Ysunza et al., 2004). Ysunza et al. (2004) primarily utilized the assessment of lateral wall motion, velopharyngeal gap size, and level of maximum displacement of the velopharyngeal sphincter. In regards to bony anatomy, Krogman et al. (1973) found that palatal clefting affects the bony structures of the cranial base and the facial skeleton. Thus, the level of the palatal plane and its relation to the cervical spine as it relates to velopharyngeal closure is of interest. Wada et al. (1997) found that the cranial base and upper cervical vertebrae growth is independent to cleft or cleft surgery effects. However, inhibition of growth at the posterior maxilla results in morphological asynchrony in upper nasopharyngeal structures and could be a sign of potential reappearance of velopharyngeal inadequacy at an older age. Satoh et al. (2002) found that lateral cephalograms identified nasopharyngeal growth and morphological changes, but no information was found regarding velopharyngeal closure. Further, Shibaski and Ross (1969) found children with repaired cleft exhibited an overall decreased growth in length and height of the maxilla in comparison to children with normal anatomy. The extent to which the above cranial variables may affect the vertical distance of VP closure relative to C1 remains unknown. It is suspected that age related pubertal changes to cranial variables in a normal population may contribute to the observed variability in the vertical distance between C1 and palatal plane that was noted in the peri-pubescent and post-pubescent age groups.

Limitations

The variability seen in the peri- and post-pubescent age groups may have resulted from the cross sectional nature of the study design. Utilizing a long term, longitudinal analysis of participants may result in a stronger relationship between age and the vertical distance between the palatal plane and C1. Increased variability noted in the peri-pubertal age group may further be exacerbated due to a smaller sample size within that age group. If analyzed longitudinally, a more consistent trend and stronger correlation between age and the vertical distance of palatal plane to C1 may be seen.

Clinical Applications and Future Research

MRI was successfully used to visualize the velopharyngeal mechanism and related anatomical structures. MRI and other 3D imaging modalities have proven to be a sound technique for the analysis of the velopharyngeal musculature as well as for the study of growth and treatment response (Atik et al., 2008; Perry, Kuehn, & Sutton, 2013; Silveira et al., 1988). MR imaging can further facilitate the diagnostic process. Measurements obtained through MRI allow information to be assessed quantitatively and non-invasively. Further, greater accuracy in craniometric measures of cranial base angle, velar length, pharyngeal depth and the level of velopharyngeal closure are possible.

The understanding and quantification of normal anatomical locations of the palatal plane and level of velopharyngeal closure relative to the cervical spine may benefit in the advancement of knowledge for the modeling and creation of a functional post-operative anatomy for individuals with VPD, especially those who undergo pharyngoplasties. Further, data suggests that utilizing the measure of vertical distance between palatal plane and C1 preoperatively may be of clinical interest in patients who undergo secondary speech surgeries due to the change in the vertical distance between these landmarks as the child ages. Future research is needed to examine the feasibility and clinical utility of using measures between C1 and palatal plane as a reference point for surgical approaches and outcomes in the cleft palate population.

Data suggests that as a child ages, specifically between the ages of 4-9, an increase in the vertical distance is observed between the anterior tubercle of C1 and the palatal plane. This may infer that for children undergoing secondary surgical treatment for VPD, the pharyngoplasty may need to be placed higher in the nasopharynx relative to C1. Secondarily, since C1 consistently resided significantly below the level of velopharyngeal closure, it can be inferred that placement of the sphincter flaps or pharyngeal flaps at C1 would result in a pharyngoplasty positioned below the level of effective VP closure. Poor surgical outcomes, secondary to placement of pharyngoplasty below the point of velopharyngeal contact, could be further exacerbated if surgical placement at C1 occurs after the age of 10, due to a greater distance between C1 and the palatal plane being present. Future research is needed to examine outcomes from pharyngoplasties relative to the data presented in the present study.

CONCLUSION

The purpose of this study was to determine if C1 remained at the same location relative to the level of velopharyngeal closure using the palatal plane as a reference line. C1 was consistently below the line of the palatal plane. Thus, the level of velopharyngeal closure resides above C1 (range 4.88mm to 10.55mm). Age was a significant predictor of the vertical distance between palatal plane and C1. Results indicated that the vertical distance between C1 and palatal plane increases as the child ages. Greater variability was observed in the vertical distance between C1 and palatal plane in the peri- and pre-pubescent age groups. Data may be extrapolated to a disordered population on further study. Additionally, longitudinal assessment is needed. Results of this study provide clinically useful information and implications for future applications to the assessment and treatment of resonance disorders. Comprehension of normal craniofacial morphology is critical to the understanding of abnormal craniofacial morphology. Normative data presented in this study provide a foundation for future comparative analyses.

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CHAPTER 4

STUDY II

Changes in the Level of Velopharyngeal Closure Relative to the Cervical Spine from Infancy through Adolescence in patients with cleft palate[2]

ABSTRACT

Objective: Palpation is often used to identify C1, an intraoperative landmark, for placement of the pharyngoplasty. However, little is known about the relationship between the palatal plane (PP) and this cervical spine landmark across select variables. This study seeks to analyze variations in the height of velopharyngeal closure relative to C1 across differing cleft types and age groups.

Design: Retrospective, cross-sectional analysis.

Setting: Large, multidisciplinary center for craniofacial disorders.

Methods: Clinical lateral cephalograms were analyzed in non-syndromic patients who underwent primary palatoplasty. Regression analysis and analysis of covariance were completed to determine how age and cleft type impact underlying cervical and velopharyngeal measures.

Results: Age and cleft type were significant predictors of the distance between the height of velopharyngeal closure and C1. Those with greater severity of clefting demonstrated larger distances between the height of velopharyngeal closure and C1. Compared to normative data, children with cleft palate have significantly larger distances between the PP and C1. The height of velopharyngeal closure above C1 was observed to range from 3.6 mm to 12.6 mm across cleft populations.

[2] Mason, K.N., Riski, J.E., Perry, J.L. (in press). Changes in the Level of Velopharyngeal Closure Relative to the Cervical Spine from Infancy through Adolescence in patients with cleft and non-cleft VPD. *Cleft Palate Craniofacial Journal.*

Conclusions: This study demonstrates the variability in C1 as a landmark across variables including cleft type and age. Due to differences in the height of velopharyngeal closure across cleft types relative to C1, it is necessary to pre-operatively quantify the vertical distance between the PP and palpable intraoperative landmark, C1, to determine the appropriate height of pharyngoplasty insertion.

INTRODUCTION

Cleft palate is the most common cause of velopharyngeal dysfunction (VPD). Approximately 20% of patients with cleft palate continue to display VPD following primary reconstruction of the palate (Bicknell et al., 2002; Riski et al., 1992). Further, there is evidence that velopharyngeal competence may diminish throughout childhood and may become unstable (Van Demark and Morris, 1983). Those with VPD are more likely than those without to develop aberrant speech and compensatory errors (Riski, 1979).

Secondary surgical treatment of VPD is often necessary following primary palatoplasty. The most common surgical methods to treat VPD are sphincter pharyngoplasty and pharyngeal flap (Cable et al., 2004; Sloan, 2000). Throughout this paper, the term pharyngoplasty will be used to refer to any surgery of the oro- or nasopharynx that involves narrowing of the velopharyngeal port whether via molding, grafting, or formation of a specified tissue, as is the case for pharyngeal flap and sphincter pharyngoplasty (LaRossa, 2000; Sloan, 2000). Literature has demonstrated similar speech outcomes across pharyngoplasty surgeries and both the sphincter pharyngoplasty and pharyngeal flap procedures have been associated with residual hypernasality or velopharyngeal obstruction (Sloan, 2000). An estimated 13-23% of patients will have a failed pharyngoplasty that will require further surgical revision (Losken et al., 2003; Witt et al., 1995; Kasten et al., 1997). Thus, treatment of resonance disorders secondary to VPD requires careful pre-operative and patient-specific planning (Marsh, 2003).

While many studies have assessed the age at which surgical repair is most successful, underlying anatomical changes related to the height of velopharyngeal closure (and prominent landmarks on the cervical spine) are less understood. Often, two of the most common causes of pharyngoplasty failure are inappropriate flap size and/or inappropriate flap placement along the posterior pharyngeal wall (PPW), such as a tissue insertion point that is below the height of velopharyngeal closure. Riski and colleagues (1984) examined 55 patients following pharyngoplasty. Analysis in that study found that approximately 50% of children demonstrated attempted velopharyngeal closure above the point of pharyngoplasty insertion. Of this group, 40% of children had continued hypernasality and residual VPD (Riski et al., 1984). Gradual development of hypernasality has been additionally evaluated by Mason and Warren (1980). Further, studies have shown when VPD is managed prior to six years of age; success reaches approximately 90% and falls between 40-70% thereafter (Leanderson et al., 1974; Riski et al., 1992). Most often, success or failure has been attributed to surgical skill and/or poor patient selection. However, the factors that contribute to post-surgical stability of the pharyngoplasty are less understood. In order to identify post-surgical changes, baseline measures of the anatomy are necessary.

Mason et al. (2016) described age related changes between the palatal plane and cervical spine in a normal population from childhood through adolescence. Further, studies have validated the use of a reference line coursing through the body of the hard palate to the posterior pharyngeal wall as an estimator of the height of velopharyngeal closure (Mason et al., 2016; Riski et al., 1984). Intraoperatively, surgeons often palpate the anterior tubercle of the first cervical vertebra (C1) to assist with placement of the pharyngoplasty. Analyses of the vertical distance, in the superior to inferior dimension, between the reference line and the anterior tubercle of C1 (Figure B1), provides a clinically useful measure. Using a cross-sectional study design, Mason et al. (2016) identified a pattern of increasing distance between the height of velopharyngeal closure and C1 as the child ages, in which the height of velopharyngeal closure was consistently above C1. This may indicate that the age at surgery is an important pre-operative consideration when determining placement of the pharyngoplasty. These hypotheses, however, are based primarily on normative, non-cleft data, and have not been examined on a clinically relevant population.

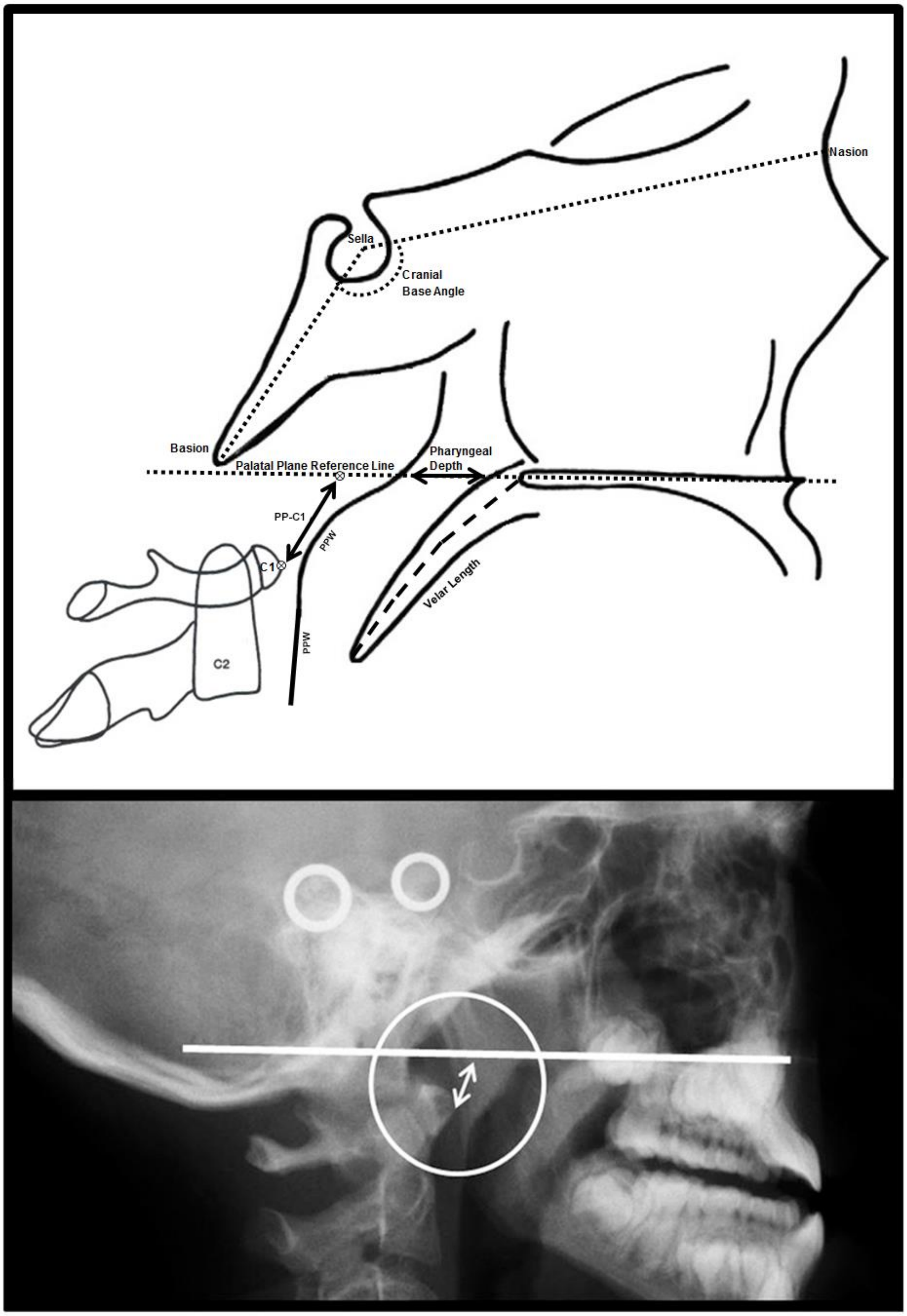

Figure B1. Schematic of measures and representation of the vertical distance between the height of velopharyngeal closure and the anterior tubercle of C1.

The purpose of this study is to revisit the analyses of Mason et al. (2016) in the context of a disordered population. It is hypothesized that similar velopharyngeal and cervical growth patterns may exist between the palatal plane and C1 in the cleft and non-cleft populations with VPD. This study seeks to analyze variations in the height of velopharyngeal closure relative to C1 across differing cleft types and age groups. Implications for a clinical population will be discussed.

METHODS

Participants

In accordance with the Children's Healthcare of Atlanta Institutional Review Board (CHOA IRB 06-196), 109 patient records were reviewed. Male and female participants (48 male, 61 female) with complete speech and imaging evaluations were selected from 18 months through adolescence (mean 7.22; SD 4.85). Participants were then categorized as syndromic or non-syndromic. The number of patients with syndromic conditions was small (N=22) and did not allow for comparison of results between the syndromic and non-syndromic groups by cleft type and were thus excluded from analysis. Lateral radiographs were also examined to ensure participants did not present with cervical spine abnormalities. Hence, only participants who were free of cervical spine anomalies and presented with non-syndromic cleft and/or non-cleft VPD were included in this analysis. This resulted in a total of 87 participants (40 male, 47 female) between the ages of 1.87 years to 20.9 years (mean 8.07; SD 5.64) with differing classifications of repaired cleft lip and palate diagnoses (Table B1). All participants completed pre-operative lateral cephalograms as part of the clinical speech evaluation.

Table B1.

Mean age within each cleft type and age group

Age Group	*Cleft Type*	*Mean Age*	*N*
Infant	UCLP	2.39 ± 0.17	4
	BCLP	2.25 ± 0.38	2
	SMC	2.91 ± 0.20	10
	CP	3.06 ± 0.19	3
	Non-Cleft VPD	2.92 ± 0.27	4
Child	UCLP	4.75 ± 0.36	7
	BCLP	5.40 ± 0.50	2
	SMC	5.44 ± 0.75	3
	CP	6.05 ± 0.28	6
	Non-Cleft VPD	5.42 ± 0.34	8
Pre-Pubescent	UCLP	9.42 ± 0.26	3
	BCLP	8.27 ± 0.38	2
	SMC	8.07 ± 0.25	6
	CP	9.14 ± 0.27	2
	Non-Cleft VPD	8.91 ± 0.45	3
Peri-Pubescent	UCLP	12.03 ± 1.62	2
	BCLP	12.13 ± 0.89	2
	SMC	11.96 ± 1.54	2
	CP	12.22 ± 1.94	2
	Non-Cleft VPD	11.90 ± 1.37	3
Adolescent	UCLP	19.12 ± 1.25	2
	BCLP	20.09 ± 1.99	2
	SMC	20.86 ± 0.36	3
	CP	18.65 ± 1.94	2
	Non-Cleft VPD	19.82 ± 1.67	2
Total		8.07 ± 5.64	87

Image Acquisition & Analyses

Lateral cephalograms were selected from data compiled by the Center for Craniofacial Disorders at Children's Healthcare of Atlanta. All participants underwent palatoplasty prior to 14 months of age and were diagnosed with VPD at the time of initial post-operative speech evaluation. Imaging was completed to evaluate velopharyngeal proportions for surgical planning. No secondary surgical management was completed on the velopharyngeal mechanism at the time the scans were collected for analyses. Cephalometric images were taken using a Gendex Orthoralix 9200 panoramic and cephalometric radiograph system.

Radiographs were imported into a digital radiographic system, Dexis (Dexis, LLC, Hatfield, PA, USA) and specified dimensions of the velopharyngeal mechanism were measured (Table B2). The measures selected in the present study represent commonly used measures reported in the literature related to craniofacial morphology (Chung et al., 1986; Johannsdottir et al., 2004; Liua etal., 2000; Mahmud, 1989; Yeong and Huggare, 2004). Image processing methods were consistent with previously reported methods within surgical, dental, and craniofacial literature (Chesters et al., 2002; Farman and Farman, 2004; Lehmann et al., 2002; Price and Noujeim, 2015). These methods involve manually identifying cranial landmarks (craniofacial and velopharyngeal features). The landmarks used in the present study further represent structures that have been routinely used due to the high frequency of detection as radiographic landmarks (Chung et al., 1986; Chung and Kau, 1985; Cotton et al., 2005; Israel, 1973; Macho, 1986; Subtelny, 1957).

Measures were obtained from the lateral image plane of a cephalometric radiograph. A description of measures is provided in Table B2 and demonstrated in Figure B1. Measures included cranial base angle, velar length, nasopharyngeal depth, and the vertical distance between the height of velopharyngeal closure (utilizing the intersection of the palatal plane with the PPW as a reference) and the anterior tubercle of C1. Cranial base angle was defined as the angle created by the intersection of the nasion-sella line and sella-basion line. Velar length was determined by measuring the linear distance between the posterior maxillary point/border of the hard palate (PMP) and center of the uvula at rest. Nasopharyngeal depth was measured by the distance between the posterior border of the hard palate/posterior maxillary point (PMP) and the posterior pharyngeal wall (PPW). PMP was delineated as the point directly below the pterygomaxillary fissure on the palatal plane. The palatal plane reference line was a line drawn through the body of the hard palate and extending posteriorly through the PPW. The linear distance between the palatal plane reference line and C1 was measured as the distance from the anterior tubercle of C1 in the inferior to superior dimension, coursing parallel to the posterior pharyngeal wall (or adenoid pad) in the region of the nasopharynx, to its intersection with the palatal plane reference line. This line correlates to the area that the surgeon would encounter intraoperatively for their incision of tissue into the posterior pharyngeal wall. The clinical and statistical significance of measures of the palatal plane and vertical distance between C1 and the height of velopharyngeal closure have been previously described by Mason et al. (2016).

Table B2.

Description of Measurements

Measure	Description
Cranial Base Angle	Angle created by the intersection of the nasion-sella line and sella-basion line.
Velar Length	Linear distance between the posterior maxillary point/border of the hard palate (PMP) and center of the tip of the uvula at rest.
Nasopharyngeal Depth (PMP to PPW)	Distance between the posterior border of the hard palate/posterior maxillary point (PMP) and the posterior pharyngeal wall (PPW). PMP delineated as point directly below the pterygomaxillary fissure on the palatal plane.
Palatal Plane Reference Line	Line drawn through the body of the hard palate and extending posteriorly through the posterior pharyngeal wall.
Distance between the Palatal Plane Reference Line and C1 (PP-C1)	Linear distance from the anterior tubercle of C1 (coursing parallel to the pharyngeal wall or adenoid pad) in the region of the nasopharynx, to its intersection with the palatal plane reference line in the inferior to superior dimension (Figure B1).

An intraclass correlation coefficient (ICC) ($\alpha = 0.05$) was used to establish interrater reliability measures. Reliability measurements were completed on 25 randomly selected radiographs by the primary and secondary raters 3 weeks after the first measures were obtained. Both raters have prior experience in measuring the areas and structures in this study. A high degree of reliability was found between measures of interest. No significant differences were noted between the primary and secondary raters. The average ICC was .892 with a 95% confidence interval ranging from .821 to .935. A Pearson product moment correlation ($\alpha = 0.05$) was used to establish intrarater reliability for the primary rater's initial measurements and primary rater's measurements completed on the 25 randomly selected cases. The intrarater reliability was excellent at $r = .962$.

Statistics

Statistical analyses were conducted with SPSS 20.0 (IBM Corp., Armonk, NY) on the 87 participants to determine age and diagnostic variations, such as cleft type, among craniometric variables. Linear regression analyses were performed to determine whether age (as a continuous variable) and diagnosis could be used to predict the vertical distance of the estimated height of velopharyngeal closure relative to C1. It was hypothesized that both age and cleft type would affect the vertical distance between the height of velopharyngeal closure relative to C1.

A two-factor analysis of covariance (ANCOVA) using the general linear model procedure in SPSS (IBM Corp.) was used to determine the interactions between age, diagnosis and the vertical distance of the estimated height of velopharyngeal closure to C1 using the covariate of race to control for the effects of racial difference on cranial measures. Patients were stratified into the following age groups: Infant/Toddler (aged 18 months-3 years), Child (4-6 years), Pre-pubescent (7-9 years), Peri-pubescent (10-14 years), and Adolescent/Post-pubescent (15-21 years). Cleft type was stratified as unilateral cleft lip and palate (UCLP), bilateral cleft lip and palate (BCLP), submucous cleft palate (SMC), cleft palate only (CP), and non-cleft velopharyngeal dysfunction (non-cleft VPD) (Table 1).

To determine how the vertical distance between the height of velopharyngeal closure and C1 differed between cleft subjects and normal participants without cleft palate, data obtained from Mason et al. (2016) on 51 typically developing non-cleft children was age matched to data from the cleft and non-cleft VPD sample discussed above. Four ANCOVAs, controlling for race, were run on each age-matched group (child, pre-pubescent, peri-pubescent and adolescent). A planned comparison (simple contrast) was completed to determine if significant differences were present for the vertical distance between the height of velopharyngeal closure and C1 for each cleft type compared to normal children.

RESULTS

Means and standard deviations are reported for craniometric measures across age groups and cleft type for all participants (Table B3). Across all age groups and diagnostic groups as a whole, the mean distance between the height of velopharyngeal closure and C1 (Table B3; noted as PP to C1) was noted to increase with a range between 3.6 mm to 12.6 mm from infancy through adolescence. In all participants, the line of the palatal plane was above C1, implying that velopharyngeal closure is achieved above C1 at all ages. The non-cleft VPD group demonstrated the smallest distance between the height of velopharyngeal closure and C1 (mean, 7.53 ± 1.72 mm). Participants with BCLP demonstrated the greatest distance between the palatal plane and C1 (mean, 9.42 ± 1.56 mm). Despite differing cleft types, cranial base angle was similar across age and diagnostic groups with a mean of 129.97 degrees. Velar length was noted to be shorter for individuals with cleft palate compared to normative data (Mason et al., 2016; Subtelny, 1957). These values are consistent with previously reported mean values for cleft populations (Wada et al., 1997; Wu et al., 1996). Nasopharyngeal depth in the cleft population was similar to normative values (Subtelny, 1957). However, individuals with non-cleft VPD demonstrated a larger nasopharyngeal depth compared to normative data.

Table B3.

Means & Standard Deviations of Velopharyngeal Measures for Age and Cleft Type

PP to C1	***UCLP***	***BCLP***	***SMC***	***CP***	***Non-Cleft VPD***	***Total***	**Normative Comparison**
Infant	7.40 ± 0.87	7.80 ± 2.68	6.78 ± 1.44	6.93 ± 0.87	6.50 ± 1.35	6.94; 1.32	N/A
Child	8.34 ± 1.13	8.85 ± 0.35	8.13 ± 2.75	9.20 ± 1.58	6.63 ± 1.51	8.02; 1.59	7.07 ± 0.33
Pre-Pubescent	8.36 ± 1.10	9.60 ± 1.01	8.20 ± 1.92	9.95 ± 2.61	8.20 ± 0.87	8.62; 1.21	7.67 ± 1.29
Peri-Pubescent	9.20 ± 1.21	9.35 ± 0.35	9.05 ± 1.06	10.30 ± 3.25	9.07 ± 1.26	9.36; 1.31	8.10 ± 1.30
Post-Pubescent	11.30 ± 1.02	11.50 ± 0.95	10.43 ± 1.81	10.80 ± 2.10	9.90 ± 1.02	10.75; 0.69	8.97 ± 1.22
Total	8.56; 1.41	9.42; 1.56	7.95; 1.63	9.21; 1.99	7.53; 1.77	8.36; 1.77	7.78 ± 1.51
Velar Length							
Infant	18.05 ± 1.73	19.35 ± 0.49	23.36 ± 4.76	24.00 ± 2.16	21.79 ± 4.06	21.30; 0.92	N/A
Child	21.14 ± 3.64	19.85 ± 5.16	23.23 ± 0.41	20.10 ± 3.52	23.47 ± 4.81	22.02; 0.83	24.39 ± 1.81
Pre-Pubescent	19.06 ± 2.88	19.10 ± 2.48	22.78 ± 2.55	19.20 ± 1.13	25.50 ± 3.19	21.86; 0.87	27.30 ± 2.47
Peri-Pubescent	20.00 ± 1.67	23.80 ± 5.37	21.60 ± 4.81	20.10 ± 1.41	26.66 ± 1.83	23.47; 1.37	28.21 ± 0.99
Post-Pubescent	32.20 ± 1.82	22.80 ± 3.75	29.06 ± 5.43	22.80 ± 2.41	32.20 ± 1.96	27.50; 2.10	32.17 ± 3.53
Total	21.79; 4.11	22.06; 4.11	21.68; 3.35	22.81; 3.67	27.92; 4.91	22.76; 4.42	27.79 ± 3.81
PMP-PPW							
Infant	12.20 ± 2.72	11.25 ± 2.33	17.03 ± 4.87	15.51 ± 2.14	18.50 ± 8.75	15.61; 1.24	N/A
Child	15.41 ± 4.74	14.60 ± 7.35	18.45 ± 3.35	14.95 ± 4.53	18.72 ± 7.38	16.54; 1.13	18.69 ± 3.43
Pre-Pubescent	18.36 ± 3.25	14.10 ± 4.12	19.70 ± 6.27	12.30 ± 1.83	19.03 ± 7.43	17.94; 1.44	19.75 ± 3.18
Peri-Pubescent	19.10 ± 4.89	18.75 ± 1.49	21.05 ± 7.00	18.90 ± 4.66	25.63 ± 7.30	21.48; 2.66	19.92 ± 2.50
Post-Pubescent	29.00 ± 3.47	23.00 ± 2.74	26.60 ± 3.46	18.30 ± 3.45	29.00 ± 6.84	26.00; 2.66	24.95 ± 4.06
Total	16.04; 5.29	16.61; 5.57	17.71; 5.45	20.53; 5.61	26.27; .13	18.37; 6.10	20.78 ± 4.17
CBA °							
Infant	131.8 ± 1.70	136.0 ± 1.41	129.5 ± 4.96	128.5 ± 5.08	131.7 ± 7.08	130.77; 4.66	N/A
Child	127.2 ± 3.82	131.0 ± 2.82	127.6 ± 3.51	128.5 ± 4.59	129.4 ± 5.87	128.53; 4.87	130.63 ± 3.35
Pre-Pubescent	131.0 ± 1.01	134.0 ± 1.86	126.8 ± 6.36	128.0 ± 2.82	130.2 ± 2.92	129.28; 4.65	130.66 ± 1.82
Peri-Pubescent	127.0 ± 1.14	130.0 ± 4.24	128.7 ± 8.13	124.0 ± 1.41	131.6 ± 4.50	130.22; 6.28	128.35 ± 4.33
Post-Pubescent	132.0 ± 1.75	126.0 ± 3.42	132.0 ± 6.92	129.0 ± 4.31	131.0 ± 3.74	132.54; 6.26	130.20 ± 2.53
Total	130.02; 4.29	131.40; 4.03	128.10; 5.60	127.50; 3.31	132.1; 5.98	129.97; 5.11	130.26 ± 2.86

PP to C1= vertical distance between the level of VP closure and C1; CBA=Cranial base angle; PMP= Posterior maxillary point; PNS= Posterior nasal spine

** Normative data obtained from Mason et al., 2016*

Multiple regression analyses were used to assess the ability of age and cleft type to predict the vertical distance between the height of velopharyngeal closure and C1. Preliminary analyses were conducted to ensure no violation of the assumptions of linearity, normality, multicollinearity, and homoscedasticity. Consistent with results from Mason et al. (2016) the effect of age was statistically significant ($p < 0.001$). The type of cleft was also significant ($p = 0.036$). The regression equations were significant predictors of the distance between the palatal plane and C1 for UCLP ($p = 0.001$), BCLP ($p = 0.008$), SMC ($p < 0.000$), CPO ($p = 0.023$), and Non-Cleft VPD ($p = 0.001$). Of these predictors, age demonstrated a higher beta value (b= 0.206, $p < 0.001$) indicating age more strongly predicts the distance between C1 and the height of velopharyngeal closure than does diagnosis ($b = -0.208$, $p = 0.036$) (Figure B2a). A moderate R-squared value ($R^2 = 0.478$) was observed for age and cleft type across all participant measures of vertical distance.

A two-way between groups analysis of covariance (Two-way ANCOVA) was completed to explore the impact of age group and diagnostic group with race treated as a covariate, on the distance between the height of velopharyngeal closure and C1. Participants were divided into five age groups (infant, child, prepubescent, peri-pubescent, and adolescent) and five diagnostic groups based on cleft type (unilateral cleft lip and palate, bilateral cleft lip and palate, submucous cleft, cleft palate only, and non-cleft VPD). The interaction between age and diagnosis was not statistically significant ($F(16,62) = 0.457$; $p = 0.958$). However, there was a statistically significant main effect for both age group ($F(4,62) = 15.15$; $p < 0.001$) and diagnostic group ($F(4,62) = 2.89$; $p = 0.029$). The estimated marginal means for age group and cleft type are displayed in Figure B2b.

Figure 2a

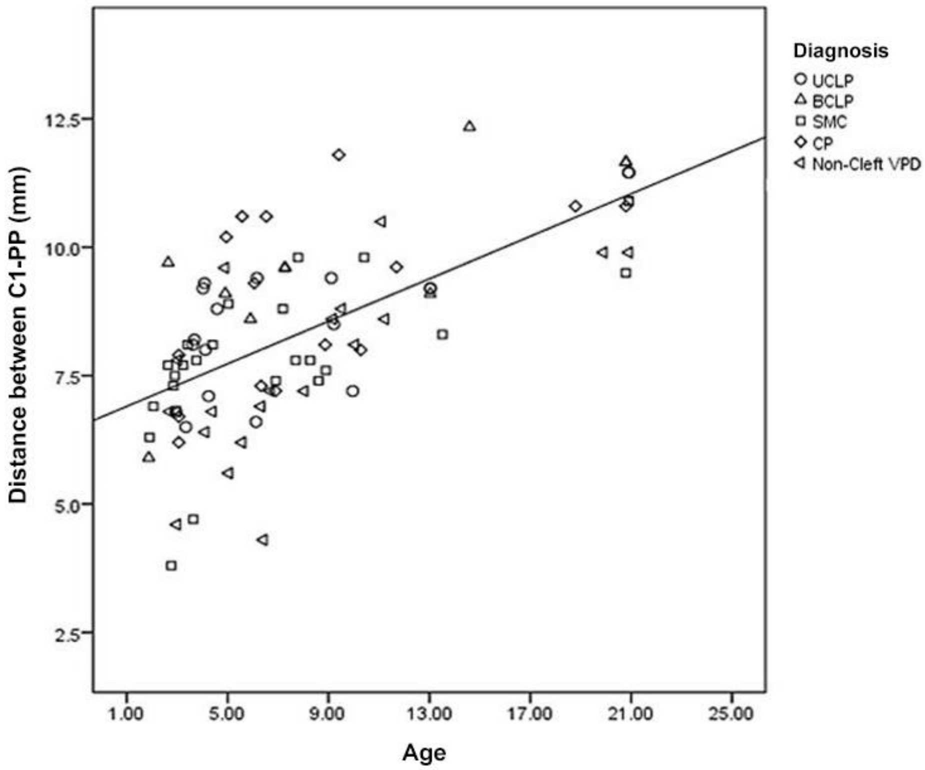

Figure 2b

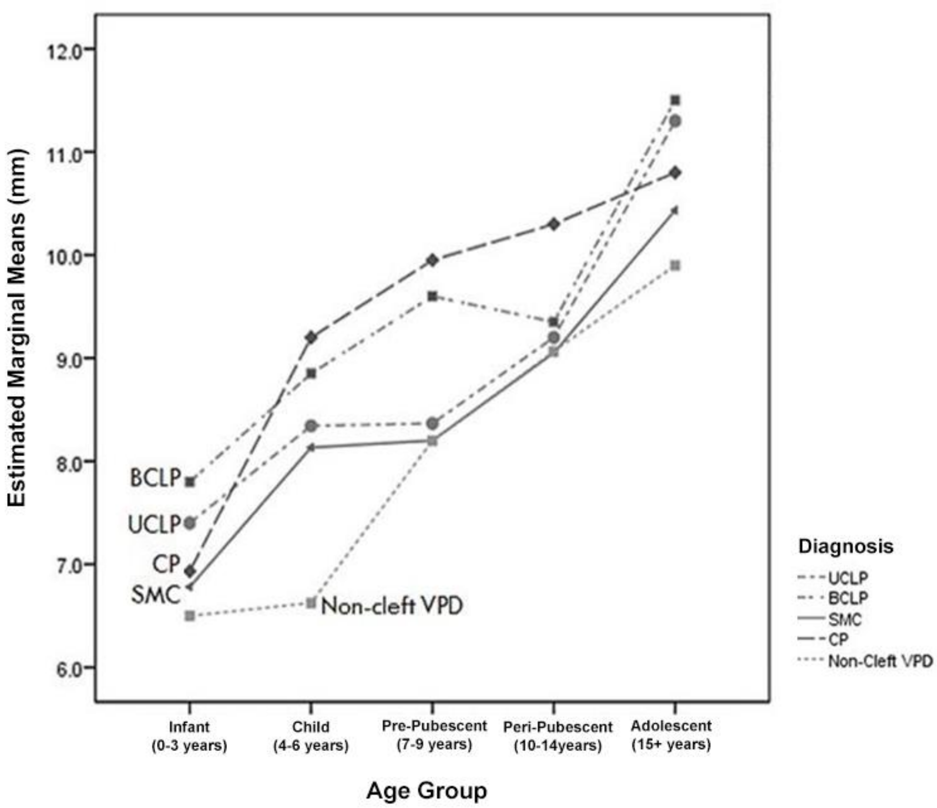

Figure B2. 2a: Scatterplot of the vertical distance between the height of velopharyngeal closure and C1 from infancy through adolescence. 2b: Estimated marginal means of the vertical distance between the height of velopharyngeal closure and C1.

A Bonferroni post-hoc test was completed to determine where differences in the mean vertical distance between the height of closure and C1 were present for age groups and diagnostic groups. Post-hoc tests indicated that the mean distance between the height of velopharyngeal closure and C1 for the infant group (mean = 7.08 mm; *SD* 0.29 mm) was significantly different from all other age groups at $\alpha = 0.05$. The child group was significantly different from the infant group ($p = 0.045$) and post-pubescent group ($p < 0.001$) and did not differ significantly from the pre- and peri-pubescent groups ($p = 1.00$ and 0.167, respectively). The adolescent group significantly differed from the child and infant groups at $\alpha = 0.05$. Individuals with BCLP, UCLP, and CP were significantly different from individuals with non-cleft VPD and SMC at $\alpha = 0.05$.

Comparison between cleft and typically developing groups revealed significant differences at $\alpha = 0.05$. A one-way ANCOVA for each age group was completed with planned comparisons (using simple contrast analysis) comparing cleft types within each age group to typically developing groups. Results indicated participants with cleft palate, of any degree, demonstrated greater distances between the height of velopharyngeal closure and C1 across all age groups compared with non-cleft, typically developing children (Table B4). Those with non-cleft VPD did not demonstrate significant differences across all age groups compared to typically developing children (p = [0.256, 0.781]). Bilateral cleft lip and palate demonstrated the greatest difference from typically developing children at each age group (p = [0.000, 0.049]). Across age groups, individuals with SMC, despite having a greater distance between the height of velopharyngeal closure and C1 compared to typically developing individuals, did not demonstrate significant differences from typically developing individuals until adolescence. By adolescence, all measures were significantly different in the cleft groups compared to normal controls (p = [0.009, 0.042]). Means, standard deviations, and significance levels for contrasts are reported in Table B4.

Table B4.

Means and standard deviations of vertical distance between the level of velopharyngeal closure and C1 (in mm)

ANCOVA	Child *p = 0.002*		Pre-Pubescent *p = 0.049*		Peri-Pubescent *p = 0.046*		Adolescent *p = 0.011*	
Normal UCLP	7.07 ± 0.33 8.34 ± 1.13	0.020*	7.67 ± 1.29 8.36 ± 1.10	0.392	8.10 ± 1.30 8.80 ± 1.47	0.045*	8.97 ± 1.22 11.30 ± 2.01	0.009**
Normal BCLP	7.07 ± 0.33 8.85 ± 1.35	0.049*	7.67 ± 1.29 9.60 ± 1.01	0.000**	8.10 ± 1.30 8.70 ± 1.28	0.034*	8.97 ± 1.22 11.50 ± 2.23	0.005**
Normal SMC	7.07 ± 0.33 8.50 ± 1.56	0.144	7.67 ± 1.29 8.21 ± 0.92	0.290	8.10 ± 1.30 9.05 ± 1.06	0.394	8.97 ± 1.22 10.43 ± 1.80	0.042**
Normal CP	7.07 ± 0.33 9.20 ± 1.58	0.001**	7.67 ± 1.29 9.95 ± 2.61	0.044*	8.10 ± 1.30 10.30 ± 3.25	0.002**	8.97 ± 1.22 10.80 ± 1.89	0.033**
Normal Non-Cleft VPD	7.07 ± 0.33 6.62 ± 1.51	0.488	7.67 ± 1.29 8.20 ± 0.88	0.416	8.10 ± 1.30 9.06 ± 1.26	0.781	8.97 ± 1.22 9.99 ± 1.49	0.256

* $p < 0.05$; ** $p < 0.01$

N= 115 (51 Controls and age matched subset of 64 Participants with cleft palate or non-cleft VPD)

DISCUSSION

Studies have demonstrated that the horizontal line of the palatal plane correlates to the height of velopharyngeal closure at its intersection with the posterior pharyngeal wall (PPW) (Losken et al., 2003; Mason et al., 2016; Satoh et al., 1999). The utilization of the height of velopharyngeal closure, in reference to the cervical spine, allows for comparison in growth and analysis of changes across the age span between cleft and non-cleft individuals. Further, Wada and colleagues (1997) demonstrated that cranial base and upper cervical vertebrae growth is independent of cleft type and surgical effects. By utilizing the palatal plane as a marker for the height of velopharyngeal closure on the PPW, along with a landmark on the cervical spine, anatomical differences that are apparent in the cleft population (such as a more posterosuperiorly displaced palate and shorter velar length) can be appropriately controlled. Thus, direct comparison of changes in the height of velopharyngeal closure can be appreciated in relation to the cervical spine in a disordered population.

Results from the present study demonstrate similar growth trends in the cleft population to that of typically developing non-cleft individuals (Mason et al., 2016) in regard to the height of velopharyngeal closure relative to the cervical spine. Statistically significant correlations were demonstrated from infancy through adolescence in the cleft population. Similar to typically developing children, as age increases, the height of velopharyngeal closure becomes higher above C1, on average. The height of velopharyngeal closure above C1 was observed to range from 3.6 mm to 12.6 mm across cleft populations. Across all cleft types, the anterior tubercle of C1 was consistently below the height of velopharyngeal closure. Variability was noted in the peri-pubescent age group, consistent with Mason and colleagues (2016). This may be explained by sex differences in the timing of pubescent changes in the nasopharyngeal cavity. The vertical descent and elongation of the pharynx, associated with an increase in vocal tract length secondary to sexual maturity, likely contributes to the growth in the distance between the two landmarks assessed within this study as well. Thus, results indicate that age is a strong predictor of the distance between the height of velopharyngeal closure and C1 in the cleft population.

By adolescence, individuals with BCLP and UCLP demonstrated the greatest distances between the height of velopharyngeal closure and C1. Variability in the growth trend was observed between individuals with BCLP and CP. Submucous cleft was found to follow a similar trend to patients with non-cleft VPD. However, significant variability was noted in the growth of the vertical distance between the height of velopharyngeal closure and C1 in the SMC population between the infant and child age groups. This is likely related to the dissimilarities in severity of submucous clefting that are typically observed (McWilliams, 1991; Mori et al., 2013).

The height of velopharyngeal closure was notably higher above C1 in the cleft population compared to the non-cleft population with the greatest difference being observed among adolescent age groups. Children in the non-cleft VPD group demonstrated a deep pharyngeal cavity which resulted in an unfavorable depth to length ratio of the pharynx and the soft palate, rather than a cleft, as the cause of VPD. Thus, the similarity this group demonstrated to typically developing children is likely due to age appropriate velar tissue (normal measures of velar length) as well as a posterior palate that has not been surgically altered. Additionally, the variation noted in velar length and reduced velar length observed in patients with cleft palate may be secondary to differing operative techniques for primary palate repair and/or hypoplasticity of the velum and velopharyngeal musculature that has previously been reported (Barr et la., 1989; Dickson, 1972; Mehendale et al., 2004). Greater height of the palatal plane on the PPW was noted by Satoh et al. (1999) and may explain why those with cleft palate demonstrated greater distances between the height of velopharyngeal closure and C1.

Those with greater distances between the height of attempted velopharyngeal closure and C1, as well as greater severity of clefting, may require a higher placed pharyngoplasty at or above the height of velopharyngeal closure. Although, prior research has indicated this necessity (Carlisle et al., 2011; Riski, 1979; Riski et al., 1984), the present study is the first to quantify the vertical distance between a prominent surgical landmark and the height of velopharyngeal closure across the age span in the cleft population. Tailoring the surgical procedure to the physiology and anatomy can improve the success of pharyngoplasties (Ysunza et al., 2004). Thus, the quantification of the vertical distance between the palatal plane and palpable intraoperative landmark (C1) is necessary preoperatively.

Limitations

Sex was not directly controlled within this sample. This would likely be an impacting factor beginning in the peri-pubescent and adolescent age groups (Kollara and Perry, 2014; Perry et al., 2014). However, the majority of data within this study were obtained in pre-pubescent children. Research has demonstrated that, prior to adolescence; males and females do not significantly differ in their craniofacial morphology (Perry et al., 2014; Ursi et al., 1993) Thus, the majority of data within this study are not likely to be affected by participant sex.

Additionally, the majority of our sample consisted of Caucasian and Hispanic participants with a smaller number of Asian and African American participants. Race was self-reported by the participants. Due to differences that have previously been reported across racial groups for velopharyngeal and craniometric variables (Kollara et al., 2015) we controlled for race in the analyses. Larger sample sizes are needed to examine the race-effect on the velopharyngeal and cervical variables of interest.

If lateral rotation in a participant's head position was present or if vertical height differences between the palatal shelves were present in repaired cleft palates, error may have been introduced, as lateral radiographic images can be considered an average of multiple sagittal slices. The palatal plane reference line was drawn through the body of the palate, however. Thus, it is unlikely that lateral rotation would have significantly affected this plane or measures relative to this plane. Further it is unlikely that rotation would have impacted any measures between C1 and the palatal plane as previous research has indicated that less than 20˚ of rotation in head and neck structures has no effect on upper airway dimensions (Jan et al., 1994). Therefore, it is unlikely that the data would be affected by this. Future studies should, however, control for any rotation when positioning participants during the imaging process.

Clinical Implications

The use of expanded imaging modalities, including radiography and magnetic resonance imaging, can improve the understanding of patterns of structural and functional changes that involve not only the velopharyngeal mechanism, but also its relationships between other cranial and cervical structures. The increasing availability of advanced imaging modalities are beneficial to further understand the underlying cause of why the vertical distance between PP and C1 is greater in those with greater severity of clefting, as well as why differences are present when comparing cleft and non-cleft individuals. In turn, future studies may lead to a deeper understanding and have implications for improved surgical intervention, insights to post-operative tissue changes, as well as alternative and, potentially, non-surgical, treatments of VPD.

CONCLUSION

The purpose of this study was to assess age related changes between the height of velopharyngeal closure and C1 across cleft type and age. Within this sample, the height of velopharyngeal closure above C1 was observed to range from 3.6 mm to 12.6 mm across cleft populations. Results indicated that greater distances were present for older children and children with greater severities of clefting. Those with greater distances between C1 and the height of velopharyngeal closure, and greater severity of clefting, may require a higher set pharyngoplasty, at or above the height of velopharyngeal closure. In order to determine the appropriate height of pharyngoplasty insertion, it may be beneficial to quantify the vertical distance between the palatal plane and a palpable intraoperative landmark (C1). Data may provide guidance for the optimal location of the pharyngoplasty and general insertion height of the sphincter flaps or incision height for the pharyngeal flap for differing cleft types from early childhood through adolescence. Thus, these patient specific measures should be quantified pre-operatively and future studies are needed to further demonstrate the clinical utility of these measures.

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CHAPTER 5

STUDY III

Relationship between Age and Diagnosis on Volumetric and Linear Velopharyngeal Measures in the Cleft and Noncleft Populations[3]

ABSTRACT

The purpose of this study was to create a 3D volumetric segmentation from MRI of the nasopharyngeal space and adenoid tissue and to examine the relationship between nasopharyngeal volume, adenoid volume, and linear measures of the velopharyngeal structures, pharynx, and vocal tract in children with and without cleft palate. Twenty-four participants including 18 typically developing children (4 to 8 years of age) and 6 children (4 to 8 years of age) with varying degrees of cleft palate were imaged using MRI. Linear and volumetric variables varied significantly based on age. Overall, nasopharyngeal volume demonstrates a modest increase with age. Nasopharyngeal volume was positively correlated with age ($p = .000$), oronasopharyngeal volume ($p = .000$), velar length ($p = .018$), and velar thickness ($p = .046$). These variables tend to increase together. Differences in nasopharyngeal volume between groups (bilateral cleft lip and palate, submucous cleft lip and palate, unilateral cleft lip and palate, and noncleft) were statistically significant ($p = 0.007$). Participants with bilateral cleft lip and palate demonstrated greater nasopharyngeal volumes than those with unilateral cleft lip and palate and submucous cleft palate.

[3] Mason, K. N., & Perry, J. L. (2016). Relationship Between Age and Diagnosis on Volumetric and Linear Velopharyngeal Measures in the Cleft and Noncleft Populations. *Journal of Craniofacial Surgery*, *27*(5), 1340-1345.

INTRODUCTION

The nasopharyngeal cavity resides above the oropharynx and occupies the superior and posterior aspect of the aerodigestive tract and vocal tract. The nasopharyngeal cavity opens anteriorly to the nasal cavity and is bounded superiorly by the sphenoid sinus, laterally by the posterior and lateral pharyngeal walls, and inferiorly by the soft palate. Variations in the dimensions of the nasopharynx are apparent from birth throughout the early ages of life. The nasopharynx size and configuration continues to change across the age span[1,2]. Similar to the vocal tract, the nasopharynx shows a steady increase in size from infancy to 15 years of age[1,3,4]. Nasopharyngeal width appears to remain consistent after two years of age while the vertical dimensions increase through adolescence[1]. Downward growth of the palate and maxilla are thought to contribute to the increase in both nasopharyngeal and nasal cavity height[1].

Nasopharyngeal volume plays an important role in maintaining patency of the upper respiratory airway. Cleft and craniofacial abnormalities frequently result in nasal deformities that alter the size, symmetry, and overall shape of the nasopharynx[5]. Examples such as septal deviation, nasal stenosis, and maxillary retrusion are potential causes of reduced nasal cavity and nasopharyngeal volume. Variation in adenoid volume and atrophy can further alter the size and shape of the nasopharynx[6]. However, absolute size of the adenoids has been reported to be less clinically relevant than the size of the adenoids relative to the nasopharynx[7-9].

Surgeries such as an adenoidectomy, primary palate repair, and pharyngoplasty may alter the nasopharyngeal volume. For example, the immediate result of a pharyngeal flap is a partially occluded velopharyngeal portal and narrowing of the transverse diameter of the nasopharyngeal passage[10]. Thus, treatment of these pharyngeal and palatal abnormalities requires accurate pre-operative measurement of the nasopharyngeal space. Studies examining the nasopharynx have commonly utilized linear and two dimensional measures to assess adenoid and nasopharyngeal dimensions[1,11-14]. However, linear measures of adenoid size using lateral radiographs have been found to overestimate the size of smaller adenoids and underestimate the size of larger adenoids[15]. Lateral cephalograms have been found to demonstrate greater variability of the nasopharyngeal airway area compared to three dimensional (3D) computed tomography images[16]. More recent developments have used 3D cone beam computed tomography to image the pharyngeal airway[17]. However, downsides to this imaging modality exist, with the most notable limitation being exposure to radiation.

The purpose of this study is to create a 3D volumetric segmentation of the nasopharyngeal space and adenoid tissue using magnetic resonance imaging (MRI) and a 3D visualization software. The relationship between nasopharyngeal volume, adenoid volume, and linear measures of the velopharyngeal structures, pharynx, and vocal tract in children (with and without cleft palate) will be discussed. Further, age related changes will be provided. It is hypothesized that adenoid and nasopharyngeal volume will follow a similar trend to linear measures of adenoid size and nasopharyngeal depth/length while providing greater clinical relevance, reliability, and detail. It is further hypothesized that significant differences in nasopharyngeal volume will be present between cleft and noncleft participants.

METHODS

Participants

In accordance with the University Medical Center Institutional Review Board (UMIRB) 24 participants were recruited to participate in the study. Of these participants, 18 were typically developing children from 4 to 8 years of age (mean age = 5.89 years of age) with an equal number of male and females (Table C1). Those classified as typically developing reported no history of craniofacial, cervical spine abnormalities, neurological, swallowing, or musculoskeletal disorders. Oral exam and a 7-point perceptual rating scale confirmed normal oral anatomy and normal resonance, respectively. Those in the cleft group were stratified based on cleft type (Table C2). Of the 24 total participants, 6 had varying degrees of cleft palate including 2 with bilateral lip and palate (BCLP), 2 with left unilateral cleft lip and palate (UCLP), and 2 with submucous cleft (SMCP) who ranged in age from 4 to 8 years of age (mean age = 5.6 years of age) and represented 2 males and 4 females (Table C1). All participants were free of syndromes, musculoskeletal, or neurological conditions. Participants with BCLP and UCLP had received primary palatoplasty and had not received a pharyngoplasty at the time of the study. Children with SMCP palate had not received a primary palatoplasty at the time of the MRI.

Table C1.

Participant Demographics

Diagnosis	***N***	***Mean Age***	***Gender***	***Caucasian***	***Hispanic***
Normal	18	5.89	Male	9	
			Female	9	
Cleft	6	5.75	Male	2	
			Female	3	1
Total	24			23	1

Table C2.

Descriptions of Measures

Measure (See Fig. C2)	Description
Nasopharyngeal Volume (NPV)	Volumetric segmentation of the space superior to the palatal plane. Borders include septum to the palatal plane. Measured in mm^3.
Oronasopharyngeal Volume (ONV)	Volumetric segmentation of the space posterior to the nasal septum and inferior to the base of the soft palate. Measured in mm^3.
Adenoid Volume (AV)	Volumetric segmentation of the adenoids across MRI slices. Measured in mm^3.
Volumetric ANR	Ratio between adenoid volume and oronasopharyngeal volume. Calculated by dividing AV/ONV.
Effective Nasopharyngeal Depth (2)	Measurement taken using the McNamera Line (ie: the shortest distance between the adenoid and palate (Major 2006).
Linear ANR	Ratio between linear measure of adenoid width and effective nasopharyngeal depth.
Pharyngeal Depth (1)	Linear measure created from line drawn from the posterior maxillary point to posterior pharyngeal wall (PMP-PPW).
Velar Length (4)	Curvilinear distance between the posterior border of the hard palate and center of the uvula at rest.
Velar Thickness (3)	Distance from the central velar point across the horizontal dimension.

Magnetic Resonance Imaging (MRI)

Procedures for MRI scanning have been previously described[18]. Participants were scanned using a Siemens 3 Tesla Trio (Erlangen, Germany) with a 12-channel Siemens Trio head coil. Previous studies have found that supine imaging data of the velopharyngeal structures can be translated to an upright activity such as speech[19-21]. Thus, a 5 minute three dimensional MRI scan was obtained while in the supine position allowing the velum to rest in a relaxed and lowered position. An elastic-fastened strap was placed around the participant's head, passing above the glabella and fastened to the head coil to reduce head motion. A high-resolution, T2-weighted turbo-spin-echo (TSE) 3D anatomical scan called Sampling Perfection with Application optimized Contrasts using different flip angle Evolution (SPACE) was used to acquire a large 3D volume covering the oropharyngeal anatomy (25.6 × 19.2 × 15.5 cm). Spatial resolution was 0.8 mm with an acquisition time of slightly less than 5 minutes (4:52). Echo time (TE) was 268 milliseconds, and repetition time (TR) was 2.5 seconds.

Image Analysis

MRI data were transferred into Amira 5.6 Visualization and Volume Modeling software (Mercury Company Systems Incorporated, Chelmsford, MA). This program is equipped with a Digital Imaging and Communications in Medicine (DICOM) support program that ensures the anatomical geometry (e.g., aspect ratio, scaling dimension, and image resolution) is maintained when importing images into the program. Planes of reference utilized include sagittal, axial, and coronal. Multiple slices within each plane of reference were analyzed to create three-dimensional segmentations (Figure C1).

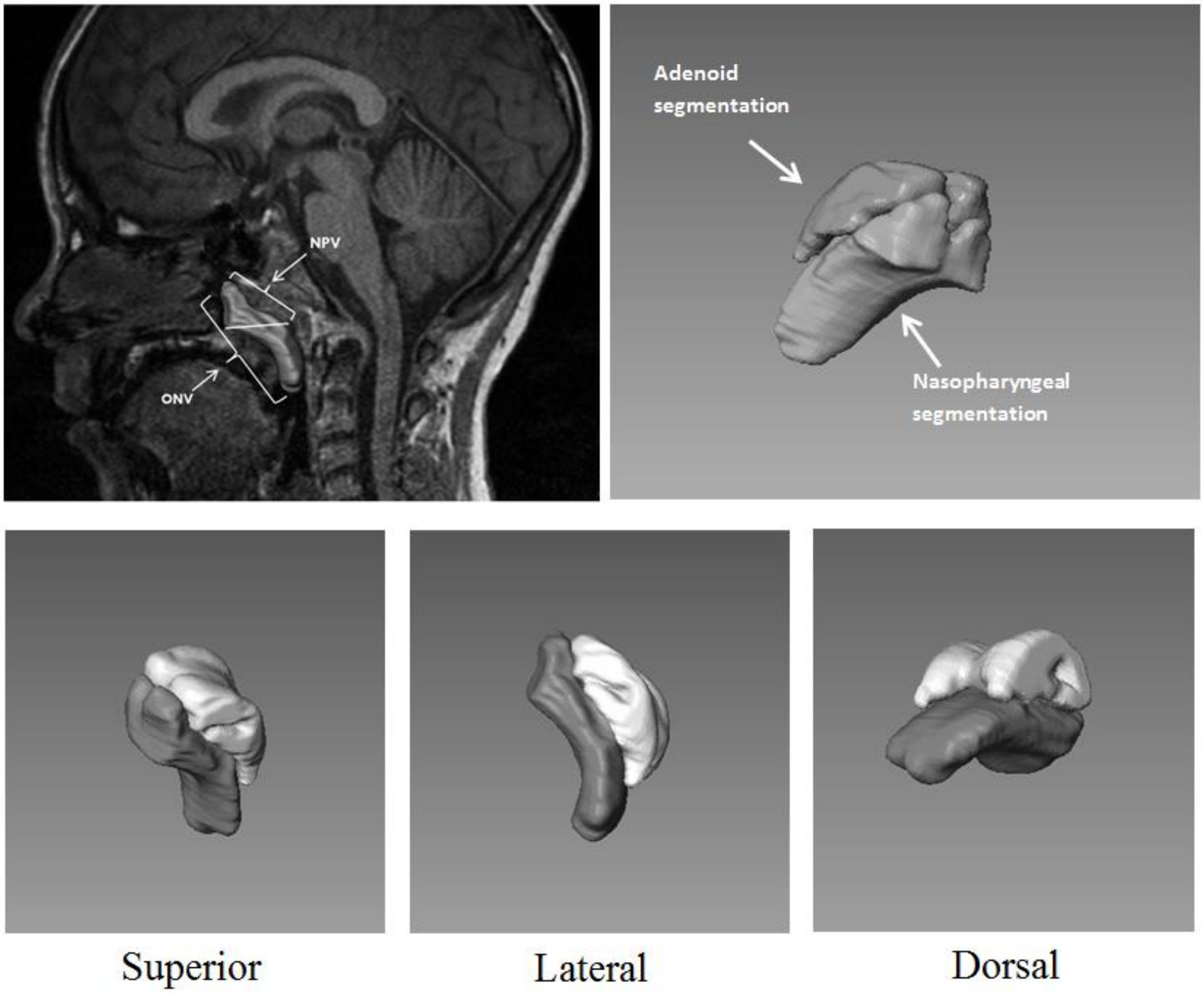

Figure C1. Demonstration of the planes of reference and segmentation of the adenoid and nasopharyngeal volumes using the 3D computerized software. ONV = oronasopharyngeal volume; NPV = nasopharyngeal volume

Statistics

Statistical analyses were conducted with SPSS 20.0 (IBM Corp., Armonk, NY) on 18 typically developing children and 6 children with cleft palate to determine age and diagnosis variations as well as interactions among linear and volumetric craniometric variables. Volumetric measures included nasopharyngeal volume, oronasopharyngeal volume, and adenoid volume.

The oronasopharyngeal and nasopharyngeal volumes were delineated by a line continuous with the palatal plane (Figure C1). Linear measures included velar thickness, velar length, effective nasopharyngeal depth, and adenoid-nasopharyngeal ratio (ANR). These variables are further described in Table C2 and displayed in Figure C2.

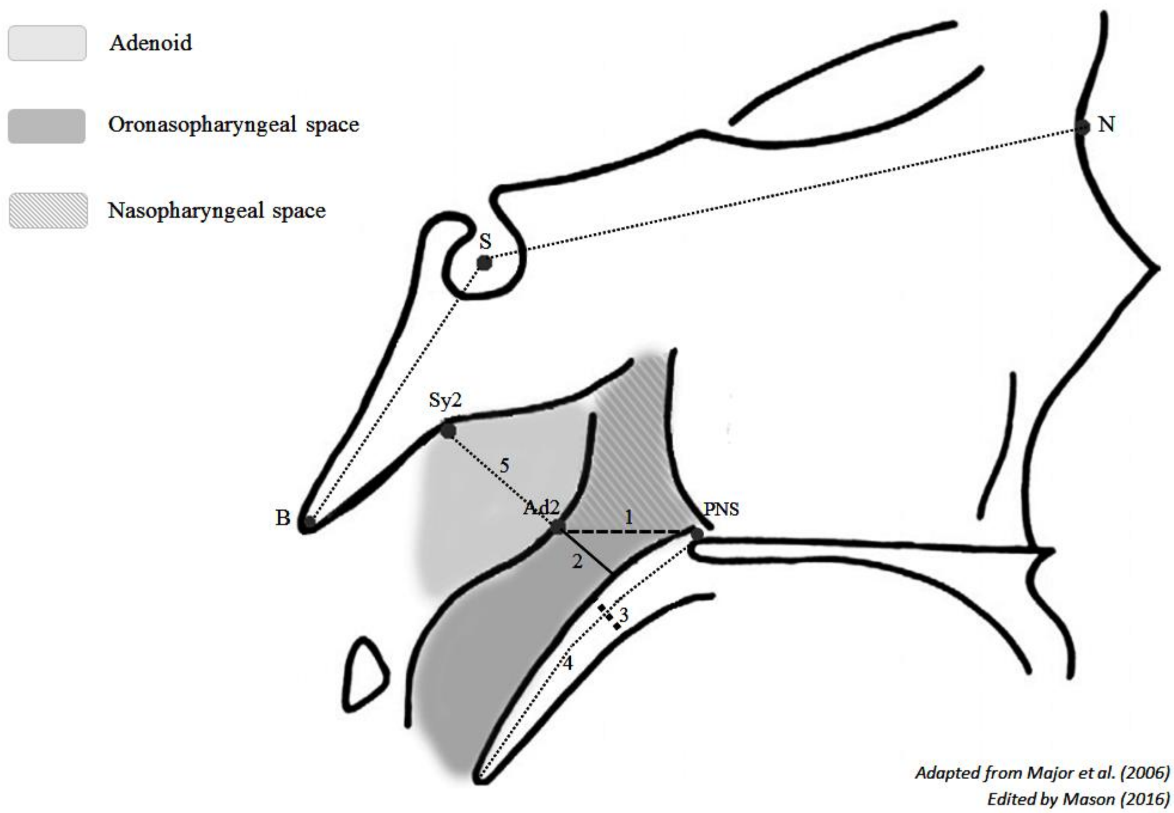

Figure C2. Representation of velopharyngeal measures and landmarks.

A bivariate correlation (Pearson product moment correlation) ($\alpha = 0.05$) was completed to determine correlations between linear and volumetric variables. A analysis of variance (ANOVA) using the general linear model procedure was used to determine the interactions between age and nasopharyngeal volume, oronasopharyngeal volume, velar thickness, and adenoid volume for the typically developing children ($n = 18$) in the sample. Utilizing the small sample of cleft participants (n = 6) (2 BCLP, 2 SMC, 2 UCLP) along with the typically developing participants (n = 18), for a total group of 24 children, an ANOVA was completed to determine if differences were present in volumetric measures between diagnostic groups.

RESULTS

Age Effects on Variables for Noncleft Participants

Volumetric mean values for nasopharyngeal volume, oronasopharyngeal volume, adenoid volume, and ANR are seen in Table C3. A two-way analysis of variance (ANOVA) was completed across age groups for noncleft participants (ages 4, 5, 6, 7, and 8 years) to determine if differences in the mean nasopharyngeal volume, oronasopharyngeal volume, and velar thickness were present between age groups. Results were statistically significant at $\alpha = 0.05$ and are enumerated in Table C4. Nasopharyngeal depth, linear ANR, velar thickness, oronasopharyngeal volume, and volumetric ANR variables all demonstrated a significant effect across age (Table C4). Figure C3 graphically represents changes in adenoid volume, nasopharyngeal volume, and oronasopharyngeal volume across the ages of 4-8 years. Growth trends for oronasopharyngeal volume demonstrate a steady increase across the selected age span. Adenoid volume showed a trend toward a decrease in overall size from 4 to 7 years of age, which increased among the 8 year old group. Overall, nasopharyngeal volume demonstrates a very modest increase with age. A Bonferoni post-hoc test revealed the greatest difference between nasopharyngeal volume occurred between the age groups of 4 and 8 years ($p = 0.004$) and 5 and 8 years ($p = 0.010$). The greatest difference in mean oronasopharyngeal volume occurred between 4 and 7 ($p = 0.029$) years and 4 and 8 years ($p = 0.003$).

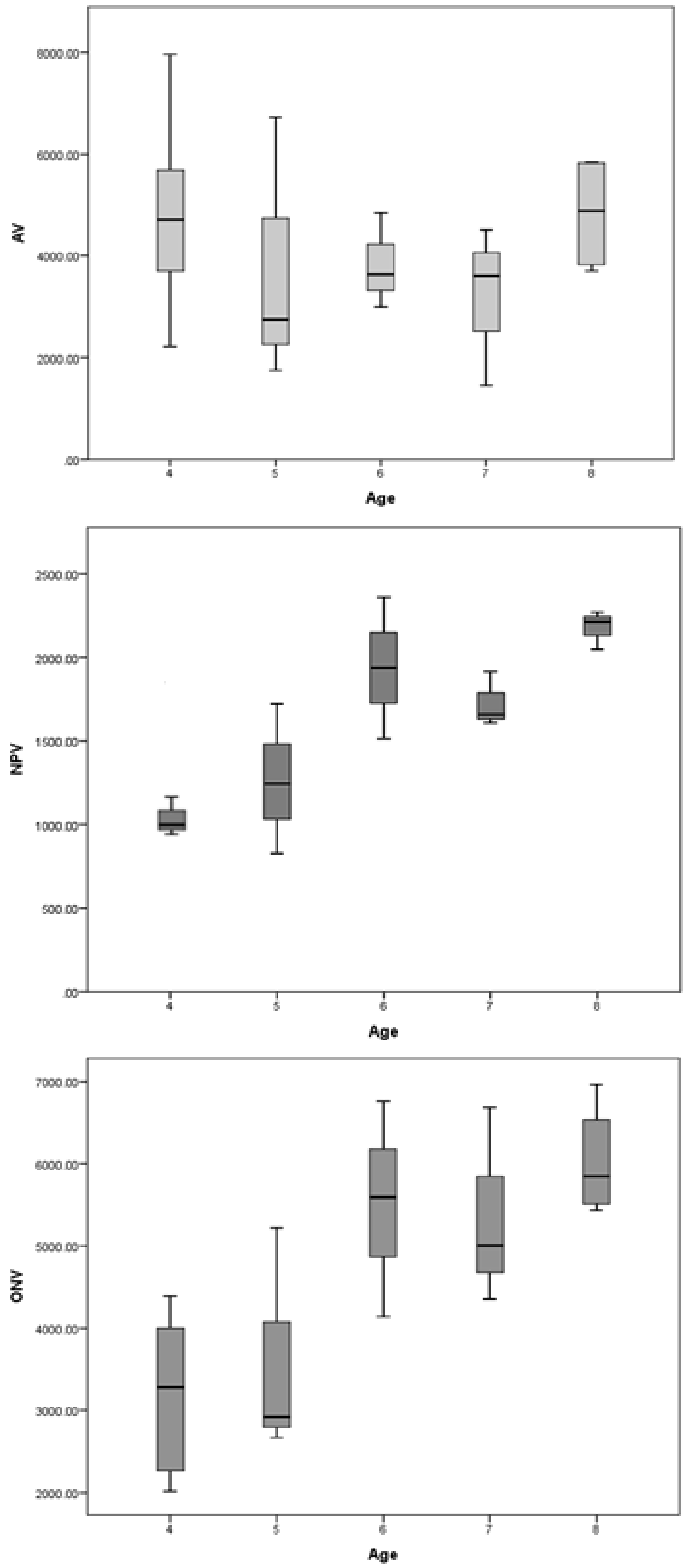

Figure C3. Boxplots demonstrating changes in AV, NPV, & ONV across age groups

Linear mean velar and craniometric variables by age for individuals with noncleft anatomy are presented in Table C3. Velar length, pharyngeal depth, and nasopharyngeal depth measures demonstrated a clear increase from 4 to 8 years of age. The ANR showed a consistent decrease, which is likely due largely to the increase in nasopharyngeal depth with age. Velar thickness showed similar values across ages 4 to 7, ranging from 6.24 to 7.26 mm. Individuals 8 years of age demonstrated a greater velar thickness (mean = 9.50 mm) compared to those in the other age ranges.

Table C3.

Linear (mm) & Volumetric (mm^3) Means Across Age Groups for Noncleft Participants

	NP Depth	Adenoid Size	Linear ANR	Pharyngeal Depth	Velar Length	Velar Thickness	NPV	ONV	AV	ANR
4 years	4.37	13.15	2.25	16.76	24.27	6.36	1168.21	3190.91	4851.73	0.71
5 years	5.35	13.29	2.50	18.01	24.53	7.26	1263.14	3601.77	3744.04	1.14
6 years	6.16	11.54	1.93	19.89	26.81	6.29	1936.77	5495.29	3824.84	1.46
7 years	7.03	9.98	1.45	19.74	27.79	6.24	1725.53	5345.63	3187.72	1.96
8 years	8.67	12.82	1.04	18.21	28.89	9.50	2185.23	6020.61	4824.99	1.28

Nasopharyngeal volume (NPV); oronasopharyngeal volume (ONV); adenoid volume (AV); ratio between adenoid volume and oronasopharyngeal volume (ANR)

Table C4.

ANOVA Results for Linear and Volumetric Measures

Linear and Volumetric Measures	***Age***		***Diagnosis***	
	F	*Sig.*	*F*	*Sig.*
NP Depth	3.526	0.002*	4.170	0.015*
Adenoid Size	2.249	0.102	0.930	0.440
Linear ANR	6.460	0.002*	0.647	0.592
CBA	0.639	0.641	5.372	0.005*
Pharyngeal Depth	0.800	0.540	2.175	0.115
Velar Length	1.794	0.172	3.647	0.026*
D:L Ratio	0.731	0.540	0.422	0.739
Velar Thickness	4.100	0.023*	0.456	0.716
Cranial Index	0.643	0.638	2.907	0.054*
NPV	6.862	0.003*	4.972	0.007*
ONV	5.079	0.011*	0.276	0.842
AV	0.649	0.634	2.134	0.120
Volumetric ANR	6.421	0.002*	1.387	0.269

* $\alpha = 0.05$

Volumetric and Linear Relationships for Noncleft Participants

Pearson product moment correlation was used to determine whether a significant linear relationship existed between nasopharyngeal volume and craniometric and velopharyngeal variables across noncleft participants. Nasopharyngeal volume was highly correlated with all variables examined demonstrating a statistically significant linear relationship (Table C5). Nasopharyngeal volume was positively correlated with age (p = .000), oronasopharyngeal volume (p = .000), cervical length (p = .004), velar length (p = .018), velar thickness (p = .046), and cranial breadth (p = .022). These variables tend to increase together. Thus, the older the child is, the greater their nasopharyngeal volume. Further, a larger cranial breadth is associated with a larger nasopharyngeal volume. The magnitude of all correlations (Table C5) is moderate-strong (moderate: $.3 < |r| < .5$; strong: $.6 < |r| < 1.0$). Stronger correlations were observed for age and oronasopharyngeal volume compared to other variables.

Table C5.

Correlations between Nasopharyngeal Volume and Craniometric-Age Related Variables

	Age	**ONPV**	**Velar Thickness**	**Velar Length**
P	0.000*	0.000*	0.046*	**0.018***
R	0.687	0.671	0.402	0.470

* $\alpha = 0.05$

Comparison of Findings to Cleft Participants

Table C6 demonstrates volumetric and linear measures across all study groups. An ANOVA was performed to determine if diagnosis (noncleft, BCLP, UCLP, SMCP) resulted in differing volumetric measures per group. Differences in nasopharyngeal volume between groups (BCLP, SMC, UCLP, noncleft) were statistically significant ($p = 0.007$). No statistically significant differences were seen for oronasopharyngeal volume and adenoid volume (Table C4). Participants with BCLP demonstrated greater nasopharyngeal volume (Table C6) than those with UCLP and SMC. Nasopharyngeal volume among those with BCLP was nearly double that of those with a diagnosis of SMC. Individuals diagnosed with SMC demonstrated the smallest values for nasopharyngeal volume, oronasopharyngeal volume, and adenoid volume. Cleft palate participants (BCLP and UCLP) demonstrated larger adenoid volume and oronasopharyngeal volume compared to those with noncleft anatomy, although not statistically significant. Children without cleft palate demonstrated the largest nasopharyngeal volume and the largest spread of nasopharyngeal volume values. Linear measures (Table C6) of pharyngeal depth, velar length and velar thickness were similar between study groups. Individuals with cleft palate (BCLP, UCLP, and SMC) displayed a greater nasopharyngeal depth and linear ANR and a decreased velar length and pharyngeal depth. Bonferroni Post-Hoc findings (seen in Table C5) demonstrate that nasopharyngeal depth and velar length varied significantly based on diagnosis. Larger study sample sizes are needed to provide greater insight into the significance of these findings in the clinical population.

Table C6.

Linear (mm) and Volumetric (mm^3) Means Across Diagnosis

	Mean Age	NP Depth	Adenoid Size	Linear ANR	Pharyngeal Depth	Velar Length	Velar Thickness	NPV	ONV	AV	ANR
BCLP	6.00	7.93	11.91	1.55	15.84	23.47	7.09	1611.22	5392.14	5100.55	1.14
SMC	5.50	8.15	13.14	1.86	15.52	24.33	6.89	869.46	4894.04	3604.54	1.38
UCLP	5.50	9.85	13.99	1.47	15.76	21.29	6.23	998.98	5148.86	5901.81	0.87
Noncleft	5.89	6.23	12.30	2.16	18.31	26.18	7.17	1631.16	4631.39	4212.69	1.24

DISCUSSION

Studies have demonstrated a growth effect of increased velar length, velar thickness, and pharyngeal depth (posterior nasal spine to pharyngeal wall) across the age span of 4 and 9 years of age[1,11,22]. Perry et al.[22] demonstrated among 85 child participants with noncleft normal anatomy a growth spurt in cranial, velar, and levator veli palatini measures between 7 and 9 years of age. These studies have been limited by two dimensional linear measures and thus do not provide a representation of the three-dimensional nature of the nasopharynx. Additionally, these studies have not discussed how structural measures (linear measures) are related to volumetric changes in the nasopharyngeal cavity.

Volumetric findings from the present study demonstrate a decrease in the adenoid volume with age, with the exception of a higher adenoid volume at the final age time point of 8 years of age. Subtelny[6] observed the adenoids to grow rapidly from infancy through two years of age and account for 50% of the nasopharyngeal airway in individuals with noncleft anatomy. After peak adenoid growth, the adenoid tissue begins to atrophy[1]. In children with noncleft anatomy, hypertrophy and hyperplasia of the adenoids occurs from 3 to 5 years of age resulting in an overall decrease in the nasopharyngeal volume[23]. It is suggested that as the adenoid volume remains constant, the nasopharyngeal volume increases with growth up until puberty when the adenoids involute[23]. Findings in the present study support this inverse relationship between nasopharyngeal volume increasing and adenoid volume decreasing with age, with the exception of those 8 years of age. At 8 years of age, child participants in the present study demonstrated an increase in nasopharyngeal volume and an increase in adenoid volume. Gangadhara Somayaji et al.[13] also observed an increase in adenoid size during 7-9 years of age followed by a decrease during 10-12 years of age. This finding may explain the gradual decrease noted in the present study for adenoid size up until the age of 8 years of age.

Findings from the present study demonstrated a very modest increase in nasopharyngeal volume and a steady increase in oronasopharyngeal volume with age among individuals with noncleft anatomy. Gangadhara Somayaji et al.[13] observed a modest increase in nasopharyngeal depth of only 3.5 mm from 4 to 9 years of age. Similarly, our findings showed an increase of 4.3 mm in nasopharyngeal depth across the age span. Significant growth trends were noted for adenoid volume (decrease with age), oronasopharyngeal volume (increase with age), and nasopharyngeal volume (increase with age) across age groups. The volume of the nasopharynx was highly correlated with all linear measures, with the strongest correlation to age, oronasopharyngeal volume, and cervical length. This was an expected finding, as it would be assumed that the volume of the nasopharynx would increase with growth of the entire pharyngeal column, as seen as increase in cervical length and age.

Subtelny[24] observed a greater nasopharyngeal width, as measured by bihamular distance, between infants with normal anatomy and infants with cleft palate. Specifically, the wider medial pterygoid plates observed in cleft participants[24] would cause the bihamular distance to be larger, thus increase nasopharyngeal volume. Subtenly[24] proposed the greater bihamular distance to be caused by the unconstrained muscular force of the pterygoid muscles exerting a lateral pull to the pterygoid plates. It is likely that the larger nasopharyngeal volume in the present study found in the BCLP group compared to all other groups can be explained by these bony structural variations observed by Subtelny[24]. Of interest, however, are the observed smaller nasopharyngeal volume mean values seen in the other two cleft groups. Smahel et al.[25] observed individuals with UCLP to have a maxilla and choanae that was significantly posterior compared to the noncleft study group. This resulted in a reduced depth of the bony nasopharynx and smaller anterioposterior nasopharyngeal airway. This may explain the smaller nasopharyngeal volume values for the UCLP group in the present study. Shibasaki and Ross[26] observed a decrease in maxillary growth among children with cleft palate. It is possible that maxillary retrusion may also lead to notably smaller nasopharyngeal volume between diagnoses compared to those with noncleft anatomy. The larger nasopharyngeal volume seen in noncleft participants may be secondary to normal maxillary relationships. Maxillary retrusion, however, was not the focus of the study.

Numerous studies have noted variations in the cranial and facial bony structures in individuals with cleft palate[26-29]. Those with cleft palate have been shown to have a superior displacement of the bony posterior hard palate compared to individuals without cleft palate[30,31]. In contrast, Subtelny[24] observed the palatal shelves to have an inferior inclination toward the floor of the mouth, rather than cranially. In either case, an abnormally positioned posterior palate would result in different nasopharyngeal to oropharyngeal volumes given the palatal plane was used as a reference line to divide the two volumes. These noted cranial differences in the maxilla and posterior palate among the literature[24,30,31] emphasize the importance of investigating the impact of surgical operations on cranial and velopharyngeal anatomy outcomes.

Stoneham (1993) suggested measurements of the nasopharynx should focus on the length of the airway rather than the actual airway diameter. Others have suggested the use of the McNamara line and measures of adenoid size to develop the ANR[13]. Major et al.[32] concluded that a limited consensus existed for identifying the most meaningful landmarks when using lateral cephalograms to measure adenoidal and nasopharyngeal tissue. Major et al.[32] suggested the use of multiple deviant measures. Three dimensional imaging modalities, such as MRI and volumetric computer software, provide the ideal visualization to identify deviant measures of the adenoids and nasopharynx without the loss of information that results from 2D measures[32]. Previous instrumentation has had difficulty quantifying the functional nasopharyngeal volume and relied primarily on qualitative analysis via nasendoscopy or two dimensional measures. This study demonstrates a valuable method for volumetric and linear measure analyses of the velopharyngeal portal.

Limitations of this study include the small sample sizes and lack of prior knowledge of surgical history on study participants. However, this sample size is similar to other reports using a similar cleft population[17,33,34]. Future studies should increase sample size. This study demonstrates a method for the nasopharyngeal volume using linear and volumetric measures. Additionally, this study demonstrates preliminary comparisons to a small cleft sample. Future studies should increase sample sizes to allow for more robust statistical analyses between cleft diagnosis. Additionally, this study did not aim to examine the relationship between nasopharyngeal volume on velopharyngeal dysfunction. It is likely that velopharyngeal dysfunction would be correlated to nasopharyngeal volumes and the ANR. Future research using larger cleft palate sample sizes should examine this association. Future research is needed to understand the impact of surgical procedures on linear and volumetric nasopharyngeal anatomies. Longitudinal growth studies using volumetric analyses in this clinical population may provide valuable insights into the growth variations between cleft and noncleft study groups.

Clinical Implications

Understanding of the underlying anatomical structures provides surgeons a clinical reference point during pre-operative planning. The use of MRI and 3D segmentation of the nasopharyngeal orifice and other pharyngeal structures, such as the adenoids, allows for a safe, non-invasive measure for the clinician to pre-operatively visualize a patient's surgical field. Further, pre- and post-operative nasopharyngeal volume can be assessed as a measure for improved speech outcomes. Larger volumes have been found to be more indicative of a residual VPI[35-37] and are often noted in more severe cleft cases such as those with BCLP. Information demonstrated within this study can additionally provide clinically useful expected measures of nasopharyngeal and adenoid volumes for reference to tailor surgical revisions and improve or reduce post-operative complications, such as obstruction, that are often seen in the case for secondary surgical management of VPI.

CONCLUSION

With increasing age, there is an inverse relationship between oronasopaharyngeal volume and adenoid volume. The nasopharyngeal volume and oronasopharyngeal volume show an increase, while the adenoid volume shows a decrease. Individuals at 8 years of age showed an increase in adenoid volume and nasopharyngeal volume compared to younger study age groups. Participants with bilateral cleft lip and palate demonstrated greater nasopharyngeal volumes than those with unilateral cleft lip and palate and submucous cleft palate. Adenoid volume was the greatest for individuals with bilateral cleft lip and palate. Individuals with cleft palate (BCLP, UCLP, and SMC) further displayed a greater nasopharyngeal depth and linear ANR and a decreased velar length. Bonferroni post-hoc findings additionally demonstrated that nasopharyngeal depth and velar length varied significantly based on diagnosis. It is likely that the observed nasopharyngeal volume variations by cleft diagnosis are due to bony structural variations in the cranium. Data provided in this study may be clinically useful in the pre-operative surgical planning process and as an outcome measure for post-operative success.

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CHAPTER 6

STUDY IV

The effects of gravity and scar contracture on post-surgical tissue changes and speech outcomes following pharyngoplasties

INTRODUCTION

The velopharyngeal mechanism requires involvement of complex muscle groups within the palate, oro- and naso-pharynx to create normal oral-nasal balance for speech. The primary velopharyngeal structures include the velum, the lateral pharyngeal walls, and the posterior pharyngeal wall. Underlying bony structures, such as the cervical spine and maxilla, exist to provide the bony framework. Palatal or velopharyngeal anomalies, such as a cleft palate, can result in an incompetent velopharyngeal mechanism, which can lead to difficulties with speech and resonance affecting communication abilities across the lifespan. Cleft palate is the most common cause of velopharyngeal dysfunction (VPD). Approximately 20% of patients following primary cleft palate repair continue to display VPD and need a secondary surgery to eliminate hypernasal speech (Bicknell, McFadden, & Curran, 2002; Riski, Ruff, Georgiade, & Barwick, 1992). Those with VPD are more likely than those without hypernasal speech post-surgically to develop aberrant speech and compensatory errors (Riski, 1979).

Common surgical methods to treat VPD are sphincter pharyngoplasty and a superior based pharyngeal flap (Cable, Canady, Karnell, Karnell, & Malick, 2004; Sloan, 2000). These surgeries are typically performed between the ages of 2-17 when VPD is observed clinically. The goal of surgery is reduce the size of the velopharyngeal portal while avoiding airway morbidity. Literature indicates similar speech outcomes for both the superiorly based pharyngeal flap and sphincter pharyngoplasty and both procedures have been associated with residual hypernasality or velopharyngeal obstruction (Argamaso et al., 1980; Peat, Albery, & Pigott, 1994; Sloan, 2000). An estimated 13-23% of patients will have a failed pharyngoplasty that will require a surgical revision (Kasten, Buchman, Stevenson, & Berger, 1997; Losken, Williams, Burstein, Malick, & Riski, 2003; Witt, Marsh, Marty-Grames, & Muntz, 1995). Secondary surgical revision is indicated when a child develops complications related to post-operative obstruction such as sleep apnea or hyponasality. A surgical revision is also indicated when the child shows no improvement in resonance (Sloan, 2000; Sommerlad et al., 1994). For the remainder of this text, pharyngoplasty will refer to the sphincter pharyngoplasty surgery.

During speech production the velum makes contact against the posterior pharyngeal wall. Among prepubescent children, the elevation of the velum occurs at the level of the palatal plane, which is a radiographic landmark running from the anterior nasal spine through the posterior nasal spine. After puberty, the velum typically elevates above the palatal plane. Riski et al. (1992b) observed the primary cause of failed pharyngoplasty was insertion of the pharyngeal flap below the point of attempted velopharyngeal contact (i.e., palatal plane) during speech production. Carlisle et al. (2011) discusses routinely placing the myomucosal flaps “as high in the nasopharynx as feasibly possible”, oftentimes resecting a portion of adenoid tissue. Others have also advised elevating the height of insertion “as high as possible” (Jackson & Silverton, 1977; Roberts & Brown, 1983) to increase success rate. However, no studies have qualified what constitutes a position that is “high enough” for proper velopharyngeal function. Furthermore, it provides no quantitative method to guide surgical planning and determine prognosis.

Based on a 15-year institution review, Riski et al. (1984) suggested a rationale for tailoring the height of flap insertion. The height of attempted velopharyngeal contact was pre-operatively identified relative to the anterior tubercle of the first cervical vertebrae. Palpation of this landmark intraoperatively assists in identifying the point that the flaps ideally should be inserted based on the predetermined height of velopharyngeal closure. Studies, however, have failed to quantify the optimal level of insertion and demonstrate a clear intra-operative approach for ensuring proper placement. In addition, due to unknown factors such as mobility of the pharyngoplasty post-surgically and the effects of scarring or growth on final tissue location, optimal insertion height may be further under-assessed.

Pre-operative surgical recommendations are typically made from perceptual judgments of resonance and imaging methods such as cephalometrics or nasendoscopy. Taking these measures a step further, magnetic resonance imaging (MRI) provides the potential for improved visualization of structures within the oro- and naso-cavities and the posterior pharynx. Magnetic resonance imaging is the only imaging modality that allows visualization of the internal musculature *in vivo*. Studies have examined the velar musculature in adults with normal anatomy (Bae, Kuehn, Conway, & Sutton, 2011; Ettema, Kuehn, Perlman, & Alperin, 2002; Perry, Kuehn, & Sutton, 2013; Tian & Redett, 2009), adults with cleft palate anatomy (Ha, Kuehn, Cohen, & Alperin, 2007), children with normal and cleft palate anatomy (Tian et al., 2010), and infants with normal and cleft palate anatomy (Kuehn, Ettema, Goldwasser, & Barkmeier, 2004; Perry, Kuehn, Sutton, Goldwasser, & Jerez, 2011). These MRI studies demonstrate the value of using MRI and the potential clinical utility to improve post-surgical speech outcomes. Imaging assessments are essential in the pre-operative evaluation process and may offer significant insight in examining the extent of migration that tissue undergoes from the time immediately post-operatively through the post-operative follow-up evaluations. It is unknown the extent to which this migration occurs and how this migration effects speech outcomes.

To the best of our knowledge, no studies have quantified post-operative changes that occur to the pharyngoplasty relative to the nasopharynx or vertebral column. Furthermore, critical barriers (radiation exposure) have limited our ability to examine the post-surgical position of the pharyngoplasty relative to the level of velopharyngeal closure in the cleft palate population. It is likely that external forces of gravity and scarring cause the pharyngoplasty to migrate inferiorly to an unfavorable location compared to the placement during surgery. The amount of inferior displacement and contributing factors to post-surgical location, however, is unknown. The purpose of this study is to examine the use of pre-operative cephalometric analyses and post-operative MRI to quantify the placement of the pharyngoplasty, visualize the nasopharyngeal airway, and examine the effect of inferior tissue migration on speech outcomes. This study is designed to bring together methodology demonstrated in studies I, II, and III to comprehensively examine the effect of external factors on a pharyngoplasty among children with VPD.

METHODS

Participant Demographics

In accordance with the approved Institutional Review Board at Children's Healthcare of Atlanta and East Carolina University (IRB #15-075), a total of 7 participants with non-syndromic, velopharyngeal dysfunction (between 4-10 years) were recruited for the study. This age group was selected based on the stages of development from childhood through adolescence and notable changes that occur with the craniofacial and skeletal development during and following puberty (Perry JL, Kollara, L, Schenck G, Fang X, Kuehn DP, Sutton, BP, in press; Perry, Kuehn, Sutton, & Gamage, 2014). Utilizing this specific age limits gender differences that may be seen between males and females in the peri- and post-pubertal stages (Perry et al., 2014;

Ursi, Trotman, McNamara, & Behrents, 1993). No significant differences have been noted across gender during this timeframe. Additionally, research has demonstrated that limited growth increments occur in nasopharyngeal height and nasopharyngeal depth over the course of a year (Handelman & Osborne, 1976). These structures correlate with the area of interest for this study. Thus, within-subjects growth between imaging time points is not a significant factor in our study population. The selected age range of participants is additionally consistent with when secondary surgeries for VPD are commonly completed. Seven participants were recruited due to the preliminary nature of the study and the long-term follow up required for each participant. To our knowledge, no studies have investigated the effects of external forces on the position of the pharyngoplasty relative to the cervical spine and palatal plane. We anticipate findings from this study will serve as pilot data for continued funding at a larger scale. Seven participants were selected for feasibility given the preliminary nature of the study. Participant demographics are outlined in Table D1. All participants received a sphincter pharyngoplasty as secondary surgical management for VPD.

Table D1.
Participant Demographics

Participant	Gender	Race	Cleft Type	Age at Initial Speech Evaluation	Age at First Surgical Intervention to the Palate	Age at Secondary Surgical Intervention	Type of Initial Palate Surgery
#1	Male	Caucasian	BCLP	5 years, 3 months	6 months	5 years, 4 months	Vomer Flap
#2	Male	Caucasian	Non-Cleft VPD	4 years, 11 months	4 years, 11 months	4 years,11 months	Sphincter pharyngoplasty
#3	Male	Hispanic	BCLP	5 years, 4 months	9 months	5 years, 10 months	Bardach 2-Flap
#4	Female	Caucasian	SMCP	9 years, 6 months	9 years, 6 months	9 years, 6 months	Furlow at time of Sphincter pharyngoplasty
#5	Male	Caucasian	SMCP	10 years, 9 months	10 years, 10 months	10 years, 10 months	Furlow at time of Sphincter pharyngoplasty
#6	Female	Caucasian	SMCP	10 years, 3 months	10 years, 4 months	10 years, 4 months	Sphincter pharyngoplasty
#7	Male	Caucasian	Non-Cleft VPD	7 years, 5 months	7 years, 7 months	7 years, 7 months	Sphincter pharyngoplasty

Inclusion/Exclusion Criteria

All children were scheduled for a pharyngoplasty from a single surgeon within the study period and between the ages of 4-10 years (*inclusion criteria*). Participant race was documented through parent report. All participants (per parent report) were free of hearing, swallowing, neuromuscular disorder/diseases, and syndromes (*exclusion criteria*).

Recruitment

Recruitment took place at the Center for Craniofacial Disorders at Children's Healthcare of Atlanta. Seven consecutive patients scheduled for pharyngoplasty were recruited to participate in the study. Participants were identified for sphincter pharyngoplasty based on established clinical criteria by clinicians at Children's Healthcare of Atlanta. The Center for Craniofacial

Disorders serves a large clinical population, with the majority of patients being derived from the state of Georgia.

Experimental Procedure

The study used a prospective, repeated measure study design for the assessment of craniometric and velopharyngeal variables pre- and post-surgically. Pre- and post-operative imaging data and speech data were collected across three time points using perceptual and instrumental evaluation tools, MRI, and cephalometric imaging.

Pre-Operative Cephalometric Imaging

Pre-operative cephalometric images were obtained from participants' medical charts. Cephalometric images are a routine imaging procedure as part of the clinical protocol using a Carestream 9300 panoramic and cephalometric imaging system. Patients at Children's Healthcare of Atlanta who are candidates for pharyngoplasties undergo cephalometric imaging as part of the routine pre-operative standard of care. Pre-operative cephalometric imaging is completed within 1-1.5 months prior to the pharyngoplasty. Lateral radiographs are taken during rest and/or during sustained phonation (sustained /s/) to evaluate the height of velar elevation or estimated level of velopharyngeal closure relative to the posterior pharyngeal wall, the adenoids, cervical spine and the dimensions of the velopharyngeal mechanism. Figure D1 demonstrates the measures obtained from cephalometric images. Cephalometric scan time lasts approximately 10 seconds. Data derived from the cephalograms was obtained from the images in the patient's clinical file.

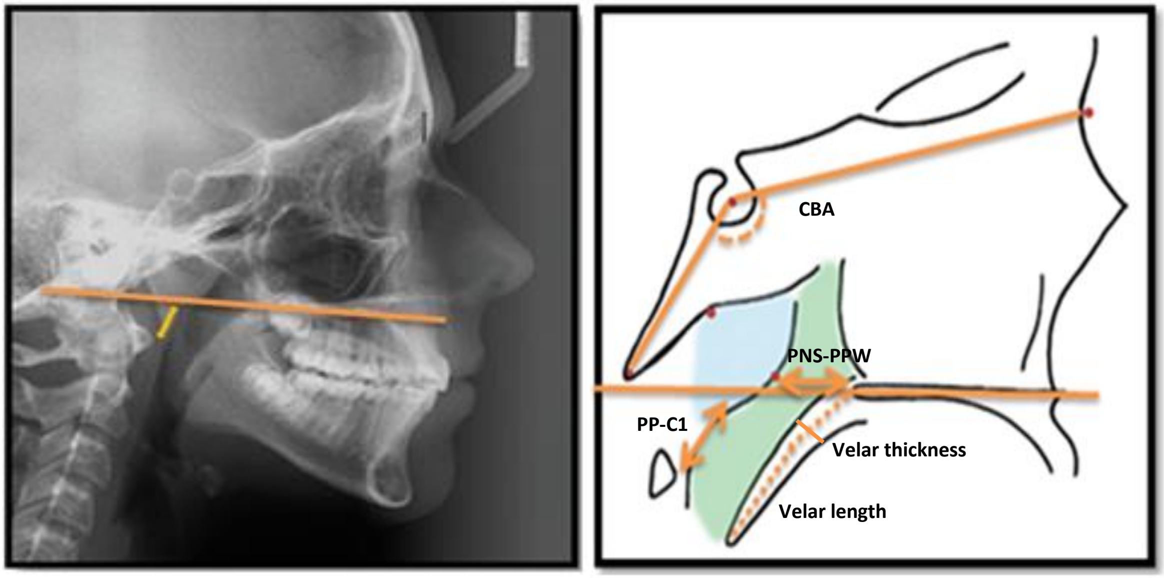


Figure D1
Example of standard 2D measures from the cephalogram

Post-Operative Research MR Imaging

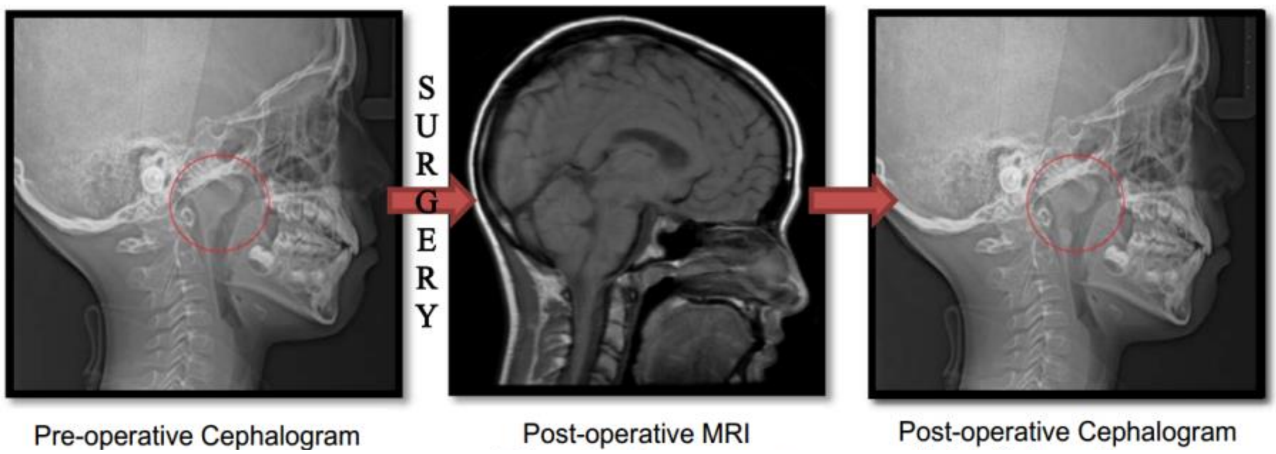
A pilot study was undertaken to establish a method for data collection and analyses that could be coordinated into the routine plan of care. Pilot data demonstrated the validity and reliability of using a developed static MRI protocol in young children between 4-10 years of age without the use of sedation. The Radiology Department at Children's Healthcare of Atlanta is equipped with a 3 Tesla research MRI magnet. Protocols for MRI magnet have previously been created by our laboratory and evaluated on Siemens and Phillips MRI scanners using young children (Kollara, Perry, & Hudson, 2015; Perry, Sutton, Kuehn, & Gamage, 2014; Perry, Kuehn, Sutton, & Fang, 2016; Schenck, Perry, & Fang, 2016). Participants in this study completed an MRI scan 1-3 days postoperatively. There was use of sedation for any of the MRI studies. The total length of the static 3D MRI scanning sequences was 3-5 minutes (this references the actual time running the MRI machine; additional time was allowed for preparing and positioning the participant. See Table D2 for the MRI scanning protocol).

Post-Operative Cephalometric Imaging

Post-surgical cephalometric imaging was conducted within the standard clinical protocol at Children's Healthcare of Atlanta 2-4 months after post-surgery for any patients deemed to have a failed surgery, using the same technique as the pre-operative cephalogram. The need for post-operative cephalometric imaging is determined by the clinicians at Children's Healthcare of Atlanta during the post-operative speech evaluation. For participants who do not have post-operative cephalograms taken as part of the clinical protocol, post-operative cephalometric scans were retrieved and analyzed from the participant's dental records.

In order to reduce exposure to radiation, no additional cephalometric images were taken for research purposes. Because of the known risks associated with radiation, only clinical scans (part of the routine clinical plan of care) were retrieved from patient medical charts and used for the purposes of this study. Thus, if cephalometric images were not needed for post-operative clinical speech assessment, lateral cephalograms were located from the participant's clinical dental records. It is standard clinical procedure to take a lateral radiograph for dental records at 6 month intervals. In addition, speech and dental reports are coordinated to occur on the same day for all patients in the craniofacial clinic at Children's Healthcare of Atlanta. Due to this, radiographs were available to be retrieved 2-4 months post-operatively from the patient's dental records. Thus, all participants received clinical post-operative imaging and the necessary post-operative data was collected. Figure 6.2 demonstrates the overall schedule for each participant including pre-operative cephalogram (~1-1.5 months pre-op), surgery, post-operative research MRI (1-3 days post-op), and post-operative cephalogram (~2-4 months post-op). Measures of interest at each time point are briefly summarized (Figure D2).

Figure D2. Sample Timeline for Image Sequencing



Data Obtained: Pre-op Image & Speech Assessment
Demographic data (race, age, surgical history)
Perceptual speech ratings
Nasometry scores
Cephalogram: Craniometric & velopharyngeal variables that will be measured from this image include:
- Velar length, velar thickness, pharyngeal depth, PP-C1, CBA, facial height.

Data Obtained: 3D MRI scan
Craniometric and velopharyngeal variables will be measured:
- Midsagittal slice: Velar length, velar thickness, pharyngeal depth, PP-C1
- Oblique Coronal Slice: Levator length, O-O, left and right angles of origin; levator volume.
- Volumetric segmentations of pharyngoplasty, tissue edema and nasopharyngeal structures.

Data Obtained: Post-op Image & Speech Assessment
Perceptual speech ratings
Nasometry scores
Cephalogram: Craniometric & velopharyngeal variables that will be measured from this image include:
- Velar length, velar thickness, pharyngeal depth, PP-C1, CBA, facial height.
- Differences in tissue changes will be calculated from pre- and post-operative measures.

Pre- and Post-Operative Speech Evaluation

All participants completed a pre- and post-operative speech evaluation through the Center for Craniofacial Disorders at Children's Healthcare of Atlanta by a single speech-language pathologist who has over 40 years of experience within this population. Perceptual speech ratings and objective, numeric, nasometric data were obtained from these evaluations. Nasometric measures were gathered using the Kay Elemetrics Nasometer II 6450 (Kay Elemetrics Corp., Lincoln Park, N.J.). Nasometry scores were obtained using standard passages (listed in Appendix 1) for oral words and sentences, nasal words and sentences, low pressure context phrases, and high pressure context phrases. Perceptual speech samples were audio recorded. Speech samples are based on a standard stimuli provided by Fletcher (1989) (Appendix A). Reliability for the perceptual speech ratings was completed using Cohen's Kappa with secondary perceptual ratings obtained from recorded speech samples by a second speech-language pathologist with experience in treating resonance disorders. A Cohen's Kappa coefficient was used to measure inter-rater agreement for the categorical ratings of hypernasality, hyponasality, velopharyngeal function, oral pressure, and audible nasal air emission pre- and post-operatively. Inter-rater reliability of perceptual speech ratings ranged from $\kappa = 0.922 - 0.964$. Near perfect agreement was seen and in cases that differed in perceptual ratings, the difference was within +/- 1 categorical measure (i.e., mild vs. mild/moderate).

Surgical Protocol

The surgical technique for the sphincter pharyngoplasty procedure differs from the Orticochea pharyngoplasty (1968) in that the palatopharyngeus muscle is inset at the point of velar contact on the posterior pharyngeal wall (Riski et al., 1984). Surgical report reflects that, in brief, patients are brought into the operating room and placed in the supine position on the operating table. General endotracheal anesthesia is then administered. After sufficient anesthesia had been reached, the patient is prepped and sterilely draped, isolating the region of the facial area. A Dingman retractor is placed in the mouth and the mouth is prepped and draped in standard surgical fashion and 0.25% Marcaine with epinephrine is injected into the posterior pharynx. A red rubber catheter is inserted through the right nostril and a silk suture is used to raise the soft palate out of the way of the area for sphincter insertion. In some cases, the soft palate may be split to visualize the posterior pharynx. At this point, a Bovie electrocautery is used to raise the left palatopharyngeus muscle with the overlying mucosa about 1.5 cm in width.

This mucosa is raised to the level of the anterior tubercle of the first cervical vertebra (C1) or above. The same procedure is performed on the right with the right palatopharyngeus muscle also raised with the overlying mucosa. A transverse incision is made in the posterior pharynx just above the level of C1. The palatopharyngeus flaps are then completely overlapped with muscle facing muscle and attached to the posterior pharyngeal fascia. The flaps are then secured with 4-0 Vicryl sutures on its contralateral sides and the mucosa anteriorly was closed with interrupted 4-0 Vicryl sutures. This results in a central opening of approximately 1 x 1.5 cm. The donor sites are then closed with interrupted 4-0 Vicryl sutures and a 22 nasal trumpet is placed through the appropriate nostril and through the sphincter opening. Following the procedure, patients are sent to the recovery room.

MRI Scanning Protocol

A high-resolution, T2-weighted, turbo spin echo (TSE), variable flip angle, 3D anatomical scan, which utilizes sampling perfection with application optimized contrasts using different flip angle evolution (SPACE), was used to acquire a large field of view covering the oropharyngeal anatomy (256x192x153.6 mm) with 0.8 mm isotropic acquired resolution (Henning, 1988; Busse et al., 2006; Siemens, 2007). Acquisition time amounted to approximately 5 minutes (4 minutes 52 seconds). The parameters of the MRI are outlined in Table D2.

Table D2
Static 3D MRI Parameters

Parameter	Description
Pulse sequence	SPACE: T2 turbo-spin-echo. Variable flip angle
Field of view	256x192x153.6mm ^{3}
Repetition time	2500ms
Echo time	268ms echo train length:171
Resolution	0.8 mm isotropic
Length of scan	4 min 52 s for 1 static volume

Behavioral Protocol Used for Research MRI

There was no use of sedation during the MR imaging process. Previously published work discusses steps to prevent potential pitfalls associated with non-sedated MRI such as claustrophobia and fear of the MRI. Steps were taken to ensure comfort of the participants throughout the exam. All patients were screened appropriately by trained MRI technicians before undergoing the MRI scan. Preliminary research has demonstrated the type of necessary environmental modifications (e.g., audio/visual stimuli, pre-MRI education/training for parents, and mock MRI simulations) that are necessary to facilitate imaging children as young as 4 years of age, without any sedation (Kollara & Perry, 2014; Perry, 2011).

A research assistant at Children's Healthcare of Atlanta, in conjunction with a Child Life specialist, was available to assist in the MRI scanning behavioral protocol. Prior to the MRI, all patients were provided with a coloring book outlining what an MRI machine is and what it does. The MRI scanners at Children's Healthcare of Atlanta were additionally equipped with mock MRI scanners to prepare participants for the scanning process as needed. All participants were acclimated to the scanning process by listening to audio samples of MRI noise in the mock scanner before beginning the scan. Participants had the ability to explore the mock scanner as

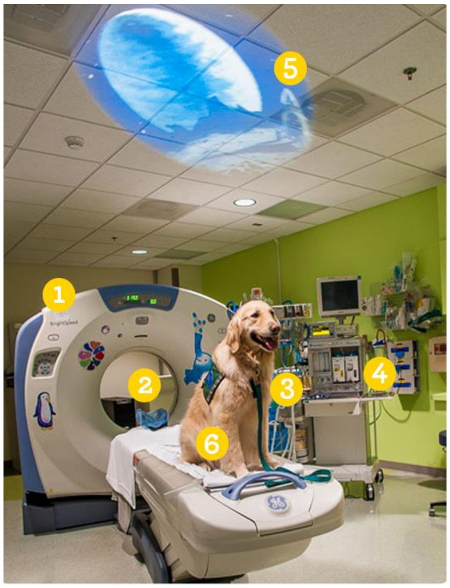


Figure D3.
MRI scanning facility at Children's Healthcare of Atlanta (image from www.choa.org)

needed. Audio and visual stimuli were present to assist with distraction during the scan. Participants were able to listen to music, watch a video, and communicate with the MRI technicians and researcher through headphones and a speaker system during the scanning process. To minimize any effects of motion and to increase comfort, participants were wrapped snugly in a warm blanket. Further, an adult (family member or researcher) was present in the scanning room with the participant for the duration of the MRI scan. This protocol has been instituted at this research site for prior collaborative studies and has had a high success rate (Figure D3).

Imaging Analysis

Cephalometric and MR images were transferred into Amira 5.6 Visualization and Volume Modeling software (Mercury Company Systems Incorporated, Chelmsford, MA). This program is equipped with a Digital Imaging and Communications in Medicine (DICOM) support program that ensures the anatomical geometry (e.g., aspect ratio, scaling dimension, and image resolution) is maintained when importing images into the program. Planes of reference utilized include sagittal, axial, and coronal. Multiple slices within each plane of reference were analyzed to create three-dimensional volumetric segmentations.

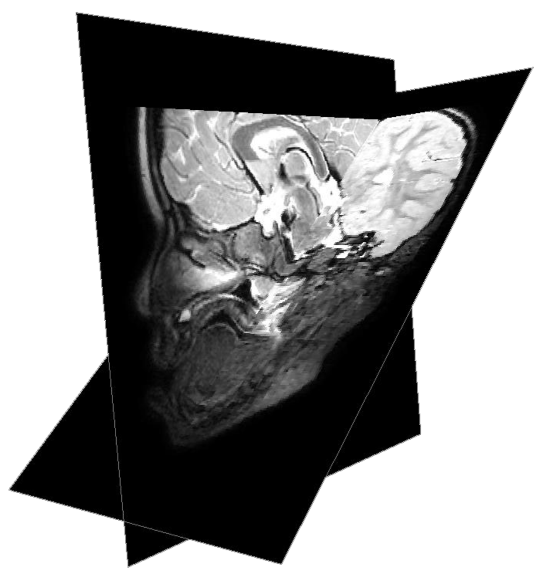


Figure D4. Example of oblique coronal plane and midsagittal plane

The midsagittal and oblique coronal MRI slices (Figure D4), as well as lateral radiographic images, were utilized to analyze craniometric and velopharyngeal variables. Tables D3 and D4 describe the measurements obtained.

Table D3.
Description of measurements obtained from cephalometric images

Measure	**Description**
Velar Length (mm)	Curvilinear distance between the posterior maxillary point/border of the hard palate (PMP) and center of the tip of the uvula at rest.
Pharyngeal Depth (PMP-PPW) (mm)	Distance between the posterior border of the hard palate/posterior maxillary point (PMP) and the posterior pharyngeal wall (PPW). PMP delineated as point directly below the pterygomaxillary fissure on the palatal plane.
Velar thickness (mm)	Distance from the central velar point across the horizontal dimension.
Cranial base angle (˚)	Angle created by the intersection of the nasion-sella line and sella-basion line
Palatal Plane Reference Line	Line drawn through the body of the hard palate and extending posteriorly through the posterior pharyngeal wall.
Vertical distance between C1 and height of VP closure (PP-C1) (mm)	Linear distance from the anterior tubercle of C1 (coursing parallel to the pharyngeal wall or adenoid pad) in the region of the nasopharynx, to its intersection with the palatal plane reference line in the inferior to superior dimension.
Final pharyngoplasty Location (Surgical insertion-C1)	Linear distance between the widest anterior point of the sphincter pharyngoplasty coursing vertically to C1.
Sphincter pharyngoplasty width (mm)	Linear width of the projection of the pharyngoplasty from the posterior pharyngeal wall at widest point.
Sphincter pharyngoplasty height (mmm)	Linear height of the sphincter pharyngoplasty tissue from dorsal to ventral side.

Table D4.

Description of measurements obtained from magnetic resonance images

Measure	Description
Nasopharyngeal volume (mm^3)	Volumetric segmentation in successive midsagittal images of the space superior to the palatal plane. Borders include septum to the palatal plane. Measured in mm^3.
Tissue edema volume (mm^3)	Volumetric segmentation in successive midsagittal images of the tissue edema against posterior pharyngeal wall from nasopharyngeal region inferiorly to the oropharynx.
Sphincter pharyngoplasty volume (mm^3)	Volumetric segmentation in successive midsagittal images of the sphincter pharyngoplasty tissue.
Sphincter pharyngoplasty width (mm)	Linear width of the sphincter pharyngoplasty tissue in the midsagittal plane at widest point.
Sphincter pharyngoplasty height (mmm)	Linear height of the sphincter pharyngoplasty tissue in the midsagittal plane from dorsal to ventral side.
Levator volume (mm^3)	Volumetric segmentation in successive oblique coronal images of the total levator veli palatine muscle. Measured in mm^3.
Left levator length (mm)	Distance from the right origin of the muscle at the base of the skull, through the middle of the muscle belly, and to the midline insertion at the velum.
Right levator length (mm)	Distance from the left origin of the muscle at the base of the skull, through the middle of the muscle belly, and to the midline insertion at the velum.
Overall levator length (mm)	Combined length of the right and left intra- and extravelar segments.
Left intravelar segment (mm)	Left length of the levator muscle that is contained within the body of the velum.
Left extravelar segment (mm)	Left insertion to origin point into the velum.
Right intravelar segment (mm)	Right length of the levator muscle that is contained within the body of the velum.
Right extravelar segment (mm)	Right insertion to origin point into the velum.
Total intravelar segment length (mm)	Entire length of the levator muscle that is contained within the body of the velum (right and left segments combined).
Total extravelar segment length (mm)	Origin to insertion point into the velum.
Levator insertion distance	Width between where the levator muscle inserts to the velum at rest and during sustained phonation.
Origin to origin distance	Width between the two attachments of the levator muscle on both temporal bones.
Right angle of origin ($^\circ$)	Angle created between a reference line connecting the two origins of the levator muscle and the line drawn to measure the levator muscle length.
Left angle of origin ($^\circ$)	Angle created between a reference line connecting the two origins of the levator muscle and the line drawn to measure the levator muscle length.
Midsagittal Surgical Insertion Height-C1	Linear distance between the widest anterior point of sphincter pharyngoplasty in the midsagittal plane coursing vertically to C1.

Statistical Analyses

Statistical analyses were conducted using IBM SPSS Version 22.0 (IBM Corp. Armonk, NY, 2012) to quantify post-operative pharyngoplasty tissue changes and how these anatomic changes impact on speech outcomes. Descriptive statistics are compiled for all variables across each imaging time point (AIM I) including measures of central tendency and standard deviation. It was hypothesized that the height of velopharyngeal closure would, on average, be greater than 5 mm above the first cervical vertebrae (Hypothesis 1). Aim I demonstrated the use of these quantitative measures during the initial pre-operative speech evaluation. Measurements of craniometric and velopharyngeal variables were completed twice on all participants, 3 days apart, to assess intra-rater reliability. Intra-class correlation coefficient (ICC) ($\alpha = 0.05$) estimates and their 95% confidence intervals was used to establish intra-rater reliability measures for anatomic variables. Reliability of measurements showed a good (defined as .75 to .90; (Portney & Watkins, 2000) to excellent agreement (defined as .90 and higher; Portney & Watkins, 2000; Table D5).

Table D5.
Intraclass Correlation Coefficient Results for Reliability Estimates

Rating 1 vs Rating 2	Average Measures ICC	95% Confidence Interval
PP-C1	.956	.924 - .980
Surgical Insertion Height – C1	.924	.884 – .960
Final Insertion Height – C1	.904	.875 – .951
Pharyngoplasty Width	.912	.842 – .943
Pharyngoplasty Height	.895	.825 – .958
Pharyngoplasty Volume	.859	.792 – .886

A measure of facial height and nasopharyngeal depth was additionally utilized to judge growth between time points. Due to the length of time between imaging time points, the effect of growth was negligible, which is a consistent finding of previous research within the study age range (Handelman & Osborne, 1976). No significant growth changes were noted for nasopharyngeal depth (p = 0.672) or facial height (p = 0.721), consistent with Handelman and Osborne (1976). These variables were chosen to reflect changes in the bony facial skeleton and soft tissue pharyngeal system. Because there was minimal-to-no growth effects between time points, growth was not factored into the statistical models.

A total of six paired samples t-tests were completed on select velopharyngeal variables of the seven participants. Paired samples t-tests were completed to assess if significant differences were present between pre- and post-operative speech outcomes as well as to examine the differences between pre-operative measures and post-operative measures for the pharyngoplasty variables of interest (AIM II). These included differences between the height of velopharyngeal closure and surgical placement of the sphincter pharyngoplasty 1-3 days post-operatively, as well as differences between 1-3 days post-operatively and ~2-4 months postoperatively. It was hypothesized that the site of the pharyngoplasty will be at or above C1 immediately following surgical placement (Hypothesis 2) and that the level of insertion of the pharyngoplasty relative to C1 will be significantly lower than that observed immediately post-operatively, when measured two to four months post-operatively (Hypothesis 3). All assumptions of for analyses using paired samples t-tests were met. The dependent variables were measured on a continuous scale. Additionally, independent variables consisted of two matched pairs and no significant outliers were present, as assessed by inspection of boxplots. Further, the variables met the assumption of normality. Table D6 presents the results of the Shapiro-Wilk test of normality.

Table D6.
Shapiro-Wilk Test of Normality

Variable	***P***	**Pass/Fail**
Height of VP closure (PP-C1)	.275	Pass
Surgical insertion height relative to C1 on MRI (mm)	.904	Pass
Final pharyngoplasty position relative to C1 on cephalogram (mm)	.521	Pass
MRI pharyngoplasty width	.525	Pass
Cephalogram pharyngoplasty width	.170	Pass
MRI pharyngoplasty height	.209	Pass
Cephalogram pharyngoplasty height	.776	Pass
Pre-operative Oral Sentence Nasometry	.524	Pass
Pre-operative Nasal Loaded Sentence Nasometry	.870	Pass
Pre-operative Sustained Nasal Nasometry	.080	Pass
Post-operative Oral Sentence Nasometry	.658	Pass
Post-operative Nasal Loaded Sentence Nasometry	.860	Pass
Post-operative Sustained Nasal Nasometry	.399	Pass

** $\alpha = 0.05$

An additional set of paired comparisons were completed to assess differences in perceptual ratings of hypernasality and velopharyngeal function pre- and post-operatively. The assumption of normality was not met for perceptual ratings of pre-operative hypernasality and pre-operative velopharyngeal function. Therefore, a nonparametric Wilcoxon signed rank test was used to determine if significant differences were present between pre- and post-operative speech ratings.

An analysis of covariance (ANOVA) was used to examine differences in speech outcomes relative to the final pharyngoplasty position. Qualitative descriptors for final pharyngoplasty location were defined as “Above C1” if they were greater than 3mm above C1, “At C1” if they were with 3mm of C1, and “Below C1” if they were greater than 3mm below C1 (Table D7). It was hypothesized that speech outcomes (nasometry scores) would be higher for individuals who demonstrated a post-operative pharyngoplasty position below the level of velopharyngeal closure (Hypothesis 4).

Table D7.

Classification of Qualitative Pharyngoplasty Location

Position	**Description**
ABOVE	Widest central portion of the pharyngoplasty is greater than 3 mm above C1.
AT	Widest central portion of the pharyngoplasty is within +/- 3 mm above or below C1.
BELOW	Widest central portion of the pharyngoplasty is greater than 3 mm below C1.

A multiple linear regression analysis and two-factor ANOVA was performed to assess if the factors of age, cleft type, and race influenced the amount of inferior movement of the pharyngoplasty (AIM III, Hypothesis 5). A volumetric segmentation of total post-operative tissue edema was completed from the MR image. The effects of the post-surgical tissue edema on final pharyngoplasty dimensions were assessed in the regression analysis. Pharyngoplasty dimensions at the two post-operative imaging time points (time points #2 and #3) and pre- and post-operative velopharyngeal portal dimensions (from time points #1 and #3) were compared using paired samples t-tests and post-operative changes are described.

RESULTS

The mean age at secondary speech surgery was 7 years, 9 months (SD = 2.47 years). The mean time between the pre-operative speech evaluation (time point #1) and post-surgical imaging (time point #2) was 3.06 months (SD = 1.08 months). The mean time between post-surgical imaging (time point #2) and post-operative follow-up (time point #3) was 3.28 months (SD = 0.76 months). Levator muscle measures were completed at time point #2, but were not factored into the analyses because lateral cephalometry (used at time point #3) does not provide muscle imaging. Means and standard deviations are reported for the variables of interest across imaging time points (Table D8).

Participants in this study demonstrated a greater than average pre-operative nasopharyngeal depth to velar length ratio compared to normative data provided by Subtelny (1957). The average nasopharyngeal depth to velar length ratio (D:L ratio) for participants in this sample was 0.85 (expected norm, 0.65). This mean is consistent with the participants' pre-operative diagnoses which included VPD related to cleft palate and non-cleft velopharyngeal insufficiency. Table C1 outlines the participant demographics, including cleft type.

All participants demonstrated a perceptual rating of velopharyngeal incompetence pre-operatively. This rating, along with nasometry scores, qualified participants to receive surgical intervention to correct VPD. Table D9 displays the pre-operative perceptual speech ratings for all participants. Perceptual ratings of pre-operative hypernasality ranged from mild/moderate to severe. All participants demonstrated pre-operative audible nasal air emission. Table D10 displays the nasometry scores for each participant. The surgical intervention type was chosen using standard clinical procedures by the treating hospital and included pre-operative clinical criteria based on the severity of clefting, amount of palatal tissue, and anatomical information from pre-operative imaging using cephalometric measures and nasendoscopy.

Table D9.
Pre-operative perceptual speech ratings for participants.

Participant	Hypernasality	VP Function	Audible Nasal Emission	Oral Pressure	Intelligibility
#1	Moderate	Inadequate	Moderate	Moderately Reduced	Mild/Moderately Reduced
#2	Moderate	Inadequate	None	Mild/Moderately Reduced	Mild/Moderately Reduced
#3	Moderate	Inadequate	Moderate	Moderately Reduced	Moderately Reduced
#4	Mild/Moderate	Inadequate	Mild	Mild/Moderately Reduced	Mildly Reduced
#5	Mild/Moderate	Inadequate	Mild/Moderate	Mild/Moderately Reduced	Mild/Moderately Reduced
#6	Moderate/Severe	Inadequate	Moderate	Moderate/Severely Reduced	Moderately Reduced
#7	Mild/Moderate	Inadequate	None	Moderately Reduced	Mild/Moderately Reduced

Table D10.
Pre-operative nasometry scores(%) for participants

Participant	Oral Sentence %	Nasal Loaded Sentence %	Sustained Nasal %
#1	43	65	94
#2	49	69	95
#3	43	58	91
#4	39	64	95
#5	33	70	97
#6	63	75	96
#7	56	78	96
Mean %	46.57 ± 10.26	68.42 ± 6.80	94.86 ± 1.95
Norm %	15.4 ± 6	61 ± 7	95 ± 3

Table D8. *Means & Standard Deviations of Participant Measures*

	2D Pre-operative Cephalometric Measures	Mean	Std. Dev.	N
IMAGING TIME POINT #1	Velar Length (mm)	22.89	0.98	7
	Pharyngeal Depth (PMP-PPW) (mm)	19.37	4.43	7
	Velar thickness (mm)	6.35	1.41	7
	Cranial base angle (˚)	129.78	2.77	7
	Vertical distance between C1 and height of VP closure (PP-C1) (mm)	5.02	0.80	7
	Surgical recommendation for placement (mm above C1)	5-10mm above	NA	7
	Pre-operative Speech Data			
	Sustained nasal sound (%)	94.86	1.95	7
	Nasal loaded sentence (%)	68.42	6.80	7
	Oral loaded sentence (%)	46.57	10.26	7
	Perceptual speech rating – Hypernasality (1-6)	4 (moderate)	0.76	7
	Perceptual speech rating – Velopharyngeal function (1-3)	3 (incompetent)	NA	7
IMAGING TIME POINT #2	**Volumetric and 2D MRI Measures**			
	Nasopharyngeal volume (mm^3)	2146.23	1033.93	3*
	Overall tissue edema volume (mm^3)	5524.39	1158.15	7
	Sphincter pharyngoplasty volume (mm^3)	849.28	187.01	7
	Sphincter pharyngoplasty width (mm)	9.75	2.72	7
	Sphincter pharyngoplasty height (mmm)	9.32	2.04	7
	Levator volume (mm^3)	510.35	187.01	7
	Overall levator length (mm)	59.70	12.20	7
	Left levator length (mm)	29.95	7.18	7
	Right levator length (mm)	29.77	5.28	7
	Left intravelar segment (mm)	9.86	3.43	7
	Left extravelar segment (mm)	19.64	4.63	7
	Right intravelar segment (mm)	9.98	2.28	7
	Right extravelar segment (mm)	19.60	3.52	7
	Total intravelar segment length (mm)	23.30	12.17	7
	Total extravelar segment length (mm)	39.25	7.98	7
	Levator insertion distance	10.43	3.45	7
	Origin to origin distance	41.42	7.67	7
	Right angle of origin (˚)	52.00	4.81	7
	Left angle of origin (˚)	53.71	5.22	7
	Difference between angles of origin (˚)	1.71	2.84	7
	Midsagittal Surgical Insertion Height-C1 (mm)	4.96	2.73	7
	Location of pharyngoplasty (at/above/below)	ABOVE ON AVERAGE		7
IMAGING TIME POINT #3	**2D Post-operative Cephalometric Measures**			
	Velar Length (mm)	21.45	2.19	7
	Pharyngeal Depth (PNS-PPW) (mm)	17.81	2.06	7
	Velar thickness (mm)	6.36	1.57	7
	Cranial base angle (˚)	128.81	2.67	7
	Surgical insertion-C1 (mm)	-1.85	3.34	7
	Vertical distance between C1 and height of VP closure (PP-C1) (mm)	5.25	0.80	7
	Sphincter pharyngoplasty width (mm)	6.79	1.30	7
	Sphincter pharyngoplasty height (mmm)	7.06	1.32	7
	Amount of inferior pharyngoplasty tissue migration (mm)	6.82	4.24	7
	Location of pharyngoplasty (at/above/below)	BELOW ON AVERAGE		7
	Post-operative Speech Data			
	Sustained nasal sound (%)	93.42	3.77	7
	Nasal loaded sentence (%)	54.00	17.21	7
	Oral loaded sentence (%)	21.00	11.53	7
	Perceptual speech rating – Hypernasality (1-6)	1.43 (normal/mild)	0.787	7
	Perceptual speech rating – Velopharyngeal function (1-3)	2.14 (adequate)	0.378	7

PMP = Posterior maxillary point; PPW = Posterior pharyngeal wall; PP = palatal plane; VP = velopharyngeal; NPV = nasopharyngeal volume

* Only 3 subjects had patency in the nasopharynx at time point #2. Thus, NPV could only be obtained on 3 participants.

AIM I: To demonstrate the use of pre-operative cephalometric and MRI analyses using visualization software to quantify the location of velopharyngeal closure relative to C1.

Use of pre-operative imaging for surgical recommendations. Paired samples t-tests were completed to assess differences between the recommended location of the pharyngoplasty (based on the pre-operative height of velopharyngeal closure) and the initial insertion site of the pharyngoplasty at time points #1 and #2 (Hypothesis 1).[4] The height of velopharyngeal closure above C1 was measured pre-operatively for each participant at time point #1. Based on this measurement, pre-operative recommendations were made to the surgeon to place the pharyngoplasty at that location on the posterior pharyngeal wall. The initial height of velopharyngeal closure was 5.02 mm above C1, on average, with a range of 3.56 – 6.67 mm above C1. A paired samples t-test was completed to determine if differences were present in the height of velopharyngeal closure at the pre-operative time point and the initial height of pharyngoplasty tissue insertion 1-3 days post-operatively. No significant differences were present between the height of velopharyngeal closure (recommended placement) and the initial tissue insertion point immediately (1-3 days) post-surgically. This indicates that the surgeon was able to utilize the pre-operative recommendation for pharyngoplasty placement (based on the height of velopharyngeal closure) and intraoperatively place the pharyngoplasty tissue above C1. Table D11 demonstrates the results of the paired samples t-test.

[4] HYPOTHESIS 1: The recommended placement of the pharyngoplasty will, on average, be greater than 5 mm above the first cervical vertebrae.

Table D11.
Paired Samples T-Test Recommendation and Surgical insertion

	N	Mean (mm)	SD	T	Significance	Result
Height of VP closure above C1 at time point #1	7	5.02	0.80	0.054	0.573	Non-significant difference
Initial tissue insertion height above C1 at time point #2	7	4.96	2.73			

** $\alpha = 0.05$

AIM II: To determine the extent of inferior migration of pharyngoplasty relative to C1 and assess the impact of tissue migration on speech outcomes.

Tissue Migration. Paired samples t-tests were completed to assess pharyngoplasty dimensions and location at time points #2 and #3. Nasometry scores and perceptual speech ratings from time points #1 and #3 were compared to determine if significant differences were present pre- and post-operatively. An ANCOVA was completed to assess the relationship between final pharyngoplasty location and speech outcome.

Initial height of tissue insertion, measured at time point #2, was compared to final post-operative pharyngoplasty location, measured at time point #3 (Hypotheses 2 and 3).[5] Significant differences were present between the initial insertion height and the final pharyngoplasty location ($p = 0.009$) (Table D12). The initial height of pharyngoplasty tissue insertion was 4.96 mm (SD = 2.73 mm) above C1, on average, ranging from 0.9 – 8.31 mm above C1. Final pharyngoplasty position was 1.85 mm below C1 (SD = 3.34 mm), on average, indicating inferior displacement of the pharyngoplasty tissue post-operatively. The amount of inferior tissue displacement varied across participants and ranged from 0.48 mm – 13.13 mm below initial tissue insertion. On average, pharyngoplasty tissue migrated inferiorly by 6.82 mm. Mean differences across all three time points can be seen in Figure D5.

[5] HYPOTHESIS 2: The site of the pharyngoplasty will be at or above C1 immediately following surgical placement. HYPOTHESIS 3: The level of insertion of the pharyngoplasty relative to C1 will be significantly lower than that observed immediately post-operatively when measured two to four months post-operatively.

Table D12.
Paired Samples T-Tests Pharyngoplasty Location (Time points #2 and #3)

	N	Mean (mm)	SD	T	Significance	Result
Initial tissue insertion height above C1 at time point #2	7	4.97	2.73	3.781	0.009**	Significant difference
Post-operative tissue location relative to C1 at time point #3	7	-1.85	3.34			

** $\alpha = 0.05$

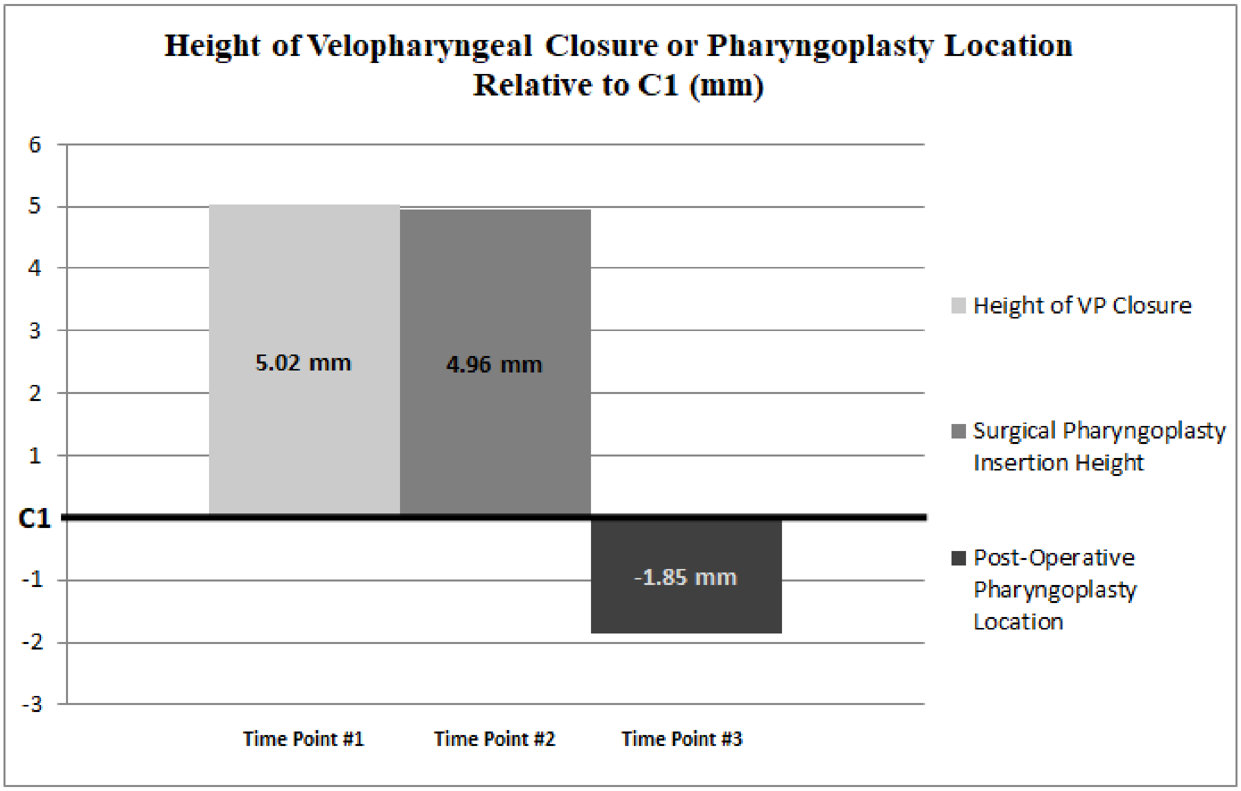


Figure D5. Mean difference for pharyngoplasty location across time points

Speech outcomes. Nasometry scores were compared to determine if differences were present between pre- and post-operative measures (time point #1 and time point #3). Significant differences were present for pre- and post-operative oral sentence nasometry scores (p = 0.003) (Table D13). Pre-operatively, the mean oral sentence nasometry score was 46.57%, which is considered to be excessive nasal resonance and outside of normative values (normative range, 15.4% ± 6%; Fletcher et al., 1989). Post-operatively, this score was 21% on average, which is at the highest threshold for normal oral resonance (Fletcher et al., 1989). No significant differences were noted for nasal loaded sentence scores (p = 0.085) or sustained nasal scores (p = 0.340). This indicates that improvements were observed in oral resonance and participants were not significantly hyponasal post-operatively. Nasometric data also demonstrated a post-operative change when compared to pre-operative scores. The mean oral nasometry percentages decreased by 25.57% following pharyngoplasty. Figure D6 demonstrates the pre- and post-operative change in nasometry scores.

Table D13
Paired Samples T-Tests Nasometry Scores (Time points #1 and #3)

	N	Mean (mm)	SD	T	Significance	Result
Pre Oral Sentence Nasometry	7	46.57	10.26	4.913	0.003**	Significant difference
Post Oral Sentence Nasometry	7	21.00	11.53			
Pre Nasal Loaded Sentence Nasometry	7	68.42	6.80	2.062	0.085	Non-significant difference
Post Nasal Loaded Sentence Nasometry	7	54.00	17.21			
Pre Sustained Nasal Nasometry	7	94.86	1.95	1.037	0.340	Non-significant difference
Post Sustained Nasal Nasometry	7	93.42	3.77			

** α = 0.05

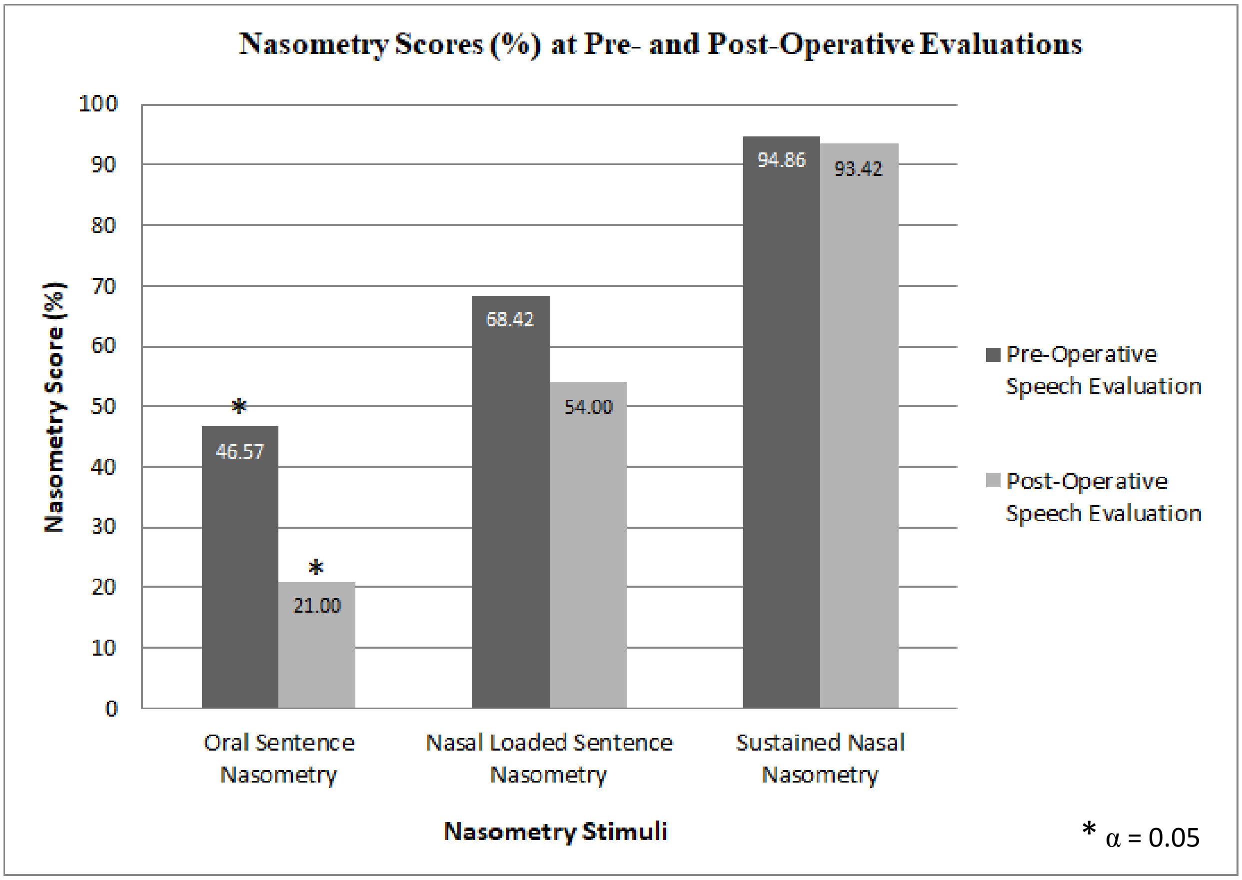


Figure D6. Pre- and post-operative nasometry scores

The assumption of normality was not met for perceptual ratings of pre-operative hypernasality and pre-operative velopharyngeal function due to pre-operative measures of velopharyngeal function being the same for all participants (inadequate) and all participants demonstrated a skewed trend for higher severity of perceptual hypernasality ratings pre-operatively. Therefore, a nonparametric Wilcoxon signed rank test was used to determine if significant differences were present between pre- and post-operative speech ratings from time points #1 and #3 (Table D14). Results indicate that significant differences were present between perceptual ratings of hypernasality ($p = 0.016$), velopharyngeal function ($p < 0.001$), oral pressure ($p = 0.011$), and audible nasal air emission ($p = 0.038$) before and after surgery. No notable outliers were present across pre- and post-operative perceptual ratings. Post-operative ratings of velopharyngeal function improved for each participant and all participants demonstrated competence or adequate velopharyngeal closure at time point #3. Post-operative hypernasality ratings from time point #3 demonstrated improvement. However, improvement was variable with post-operative ratings of hypernasality ranging from normal to mild across the seven participants.

Table D14

Nonparametric Wilcoxon Signed Rank Related Samples Test Results

Perceptual Speech Ratings	**N**	**Mean**	**SD**	**Standardized Test Statistic**	**Significance**	**Result**
Pre Perceptual Hypernasality Rating	7	3.71 (Moderate)	0.75	-2.414	0.016**	Significant difference
Post Perceptual Hypernasality Rating	7	1.71 (Normal-Mild)	0.95			
Pre Velopharyngeal Function Rating	7	4.0 (Incompetent)	0.00	-2.530	< 0.001**	Significant difference
Post Velopharyngeal Function Rating	7	2.14 (Adequate)	0.38			
Pre Perceptual Oral Pressure Rating	7	3.57 (Moderately reduced)	0.79	-2.530	0.011**	Significant difference
Post Perceptual Oral Pressure Rating	7	1.29 (Normal)	0.49			
Pre Audible Nasal Air Emission Rating	7	2.71 (Mild-Moderate)	1.38	-2.070	0.038**	Significant difference
Post Audible Nasal Air Emission Rating	7	1.57 (Mild)	0.79			

** $\alpha = 0.05$

An analysis of covariance (ANCOVA) was used to examine differences in speech outcomes relative to the final pharyngoplasty position (Hypothesis 4).[6] Significant differences were present for oral sentence nasometry scores (F = 27.264; p = 0.003) relative to the final pharyngoplasty location (Table D15). Three participants had a final pharyngoplasty location "at" or "above" C1 and oral sentence nasometry scores that fell within normal limits (9-11% respectively). Four subjects demonstrated a final pharyngoplasty position "below" C1 and had nasometry scores above normal limits (23-38%, respectively). Those with a final pharyngoplasty location below the level of C1 demonstrated worse oral resonance (Figure D7). This indicates that the final position of the pharyngoplasty was predictive of resonance outcomes at the final study time point of approximately three months post-surgically. The expected range for normal oral sentence nasometry scores are 15.4% ± 6% (Fletcher et al., 1989; Pegoraro-Krook et al., 2006). The four participants who demonstrated the highest post-operative oral sentence nasometry scores also demonstrated the greatest amount of inferior tissue migration of the pharyngoplasty (8.21 – 12.00 mm range).

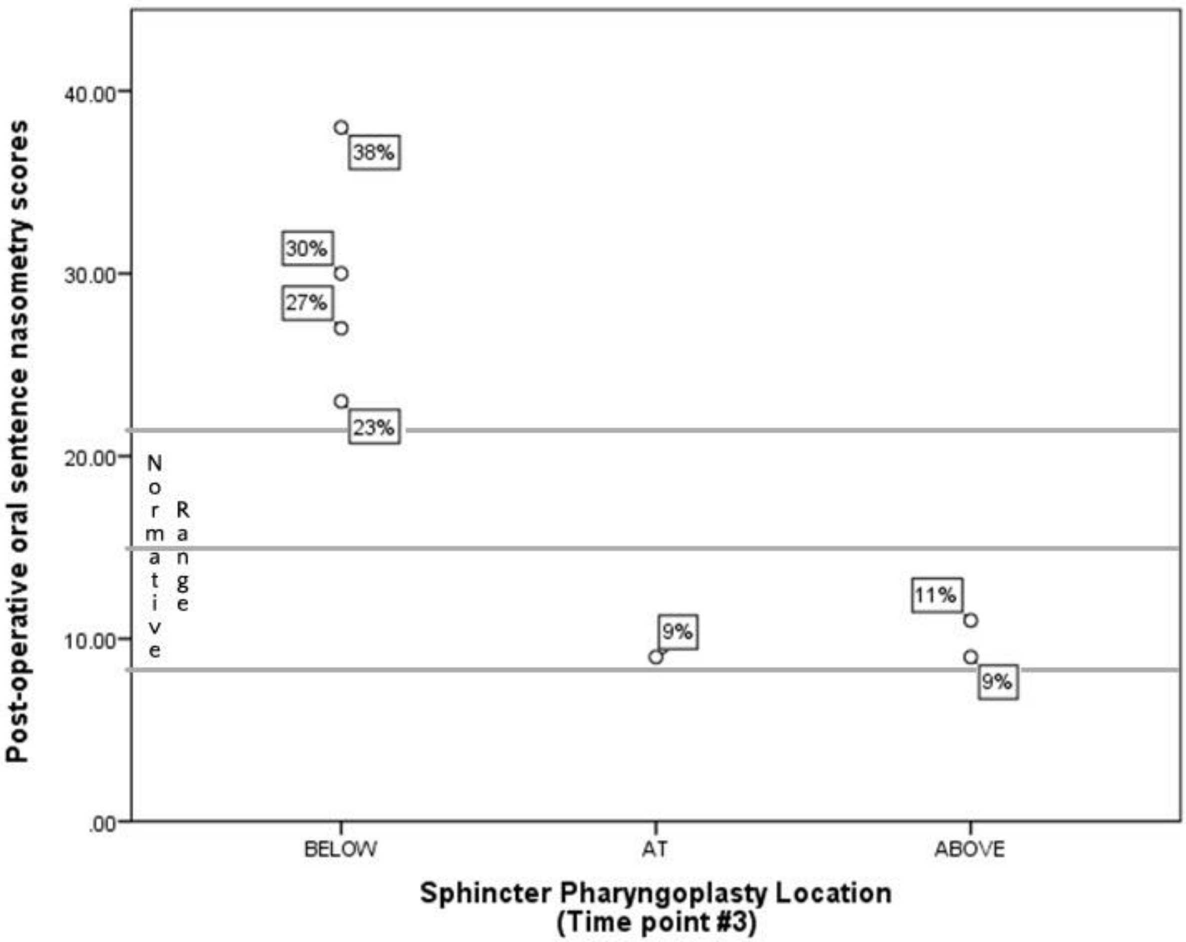
Table D15.
ANCOVA for Final Pharyngoplasty Location and Speech Outcomes

	P	F
Oral Loaded Sentence Nasometry	0.020**	20.732
Nasal Loaded Sentence Nasometry	0.791	0.084
Sustained Nasal Nasometry	0.328	1.357

** α = 0.05

[6] HYPOTHESIS 4: Speech outcomes (nasometry scores) will be higher for individuals who demonstrate a post-operative pharyngoplasty position below the level of velopharyngeal closure.

Figure D7. Oral Sentence Nasometry Scores Relative to Final Pharyngoplasty Location



AIM III: To quantify dimensions of the post-operative 3D nasopharyngeal airway and assess factors that show trends in influencing post-surgical tissue location.

Predictors of tissue migration. Analyses were performed to assess if the factors of age, cleft type, and race influenced the amount of inferior movement of the pharyngoplasty (Hypothesis 5).[7] Additional factors in the models included pharyngoplasty volume and amount of post-operative tissue edema. A multiple regression analysis was used to assess if age, pharyngoplasty volume, and post-operative tissue edema were predictive of the amount of

[7] HYPOTHESIS 5: The factors of cleft type, age, race, or velopharyngeal dimensions will be predictive of the amount of tissue displacement observed post-operatively.

pharyngoplasty tissue migration. A two-factor ANOVA was completed to assess if the factors of race and cleft type impacted the amount of inferior tissue migration. None of the predictor variables resulted in a significant regression equation (F = 2.987; p = 0.412) with an R^2 of 0.968. Within this sample, neither age (p = 0.285), cleft type (p = 0.591), or race (p = 0.893) were significant predictors. Pharyngoplasty volume (p = 0.335) and post-operative tissue edema (p = 0.247) were additionally non-significant predictors of the amount of inferior movement. However, two of the four participants who demonstrated worse oral nasometry scores and more inferior movement of the pharyngoplasty were noted to have BCLP. The two participants with BCLP demonstrated the largest pharyngoplasty volumes as well as the largest post-operative decrease (10.97 mm and 12.00 mm, respectively) from pharyngoplasty insertion height to final pharyngoplasty position.

All participants demonstrated notable post-operative tissue edema, with only three demonstrating any post-operative patency of the nasopharyngeal space (Figure D8). Cephalometric imaging at time-point #3 revealed resolution of post-surgical tissue edema and patency of the nasopharyngeal airway.

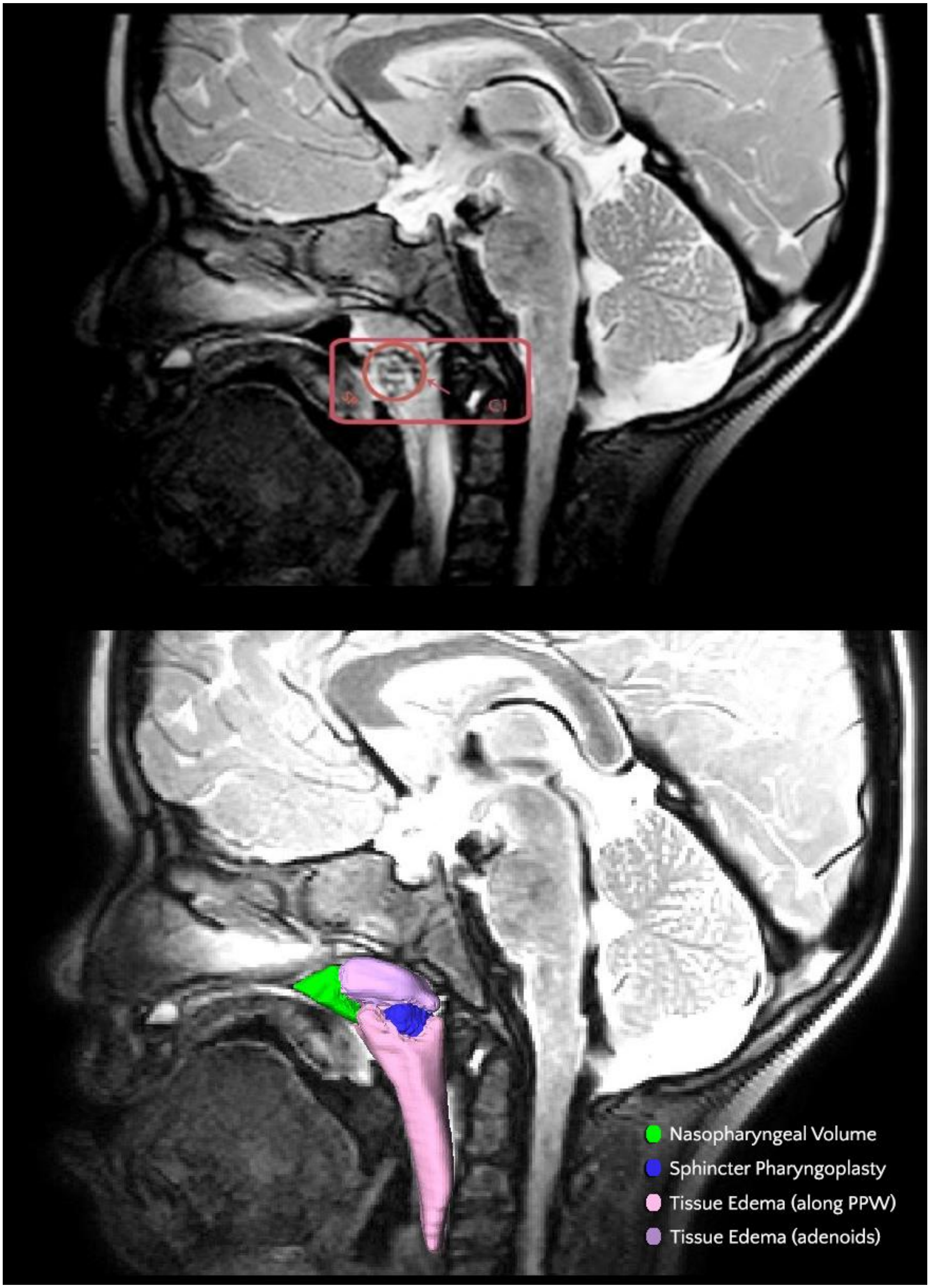


Figure D8
Visualization of the post-operative pharyngeal airway (top) with volumetric segmentations (bottom) of tissue edema (pink), the patent nasopharyngeal space (green), and pharyngoplasty tissue (blue).

Post-operative pharyngoplasty dimensions. To assess if differences were present in overall pharyngoplasty size between the two post-operative imaging time points, a volumetric segmentation was completed of the pharyngoplasty tissue from the MRI scan at time point #2. Pharyngoplasty volume was 849.28 mm^3 ± 187.01 mm^3 at time point #2. All volumetric segmentations of the pharyngoplasty indicated a cohesive tissue mass with no midline separation. Due to the 3D nature of the MRI and 2D nature of the cephalogram, a Pearson correlation coefficient was used to correlate the measure of pharyngoplasty volume to 2D measures of the pharyngoplasty (Figure D9). This allowed for direct comparisons of measurements between the imaging modalities at time points #2 and #3. Pharyngoplasty volume was significantly correlated to the measure of pharyngoplasty width (p = 0.025) (Table D16). Therefore, to assess differences in pharyngoplasty size, the measure of pharyngoplasty width was compared at time point #2 and time point #3.

Table D16.
Correlation between measures of pharyngoplasty dimensions

		Pharyngoplasty Width	Pharyngoplasty Height	Pharyngoplasty Volume
Pharyngoplasty Width	Pearson Correlation	1	.816*	.810*
	Sig. (2-tailed)		.025	.027
	N	7	7	7
Pharyngoplasty Height	Pearson Correlation	.816*	1	.616
	Sig. (2-tailed)	.025		.141
	N	7	7	7
Pharyngoplasty Volume	Pearson Correlation	.810*	.616	1
	Sig. (2-tailed)	.027	.141	
	N	7	7	7

* Correlation is significant at the $\alpha = 0.05$ level (2-tailed)

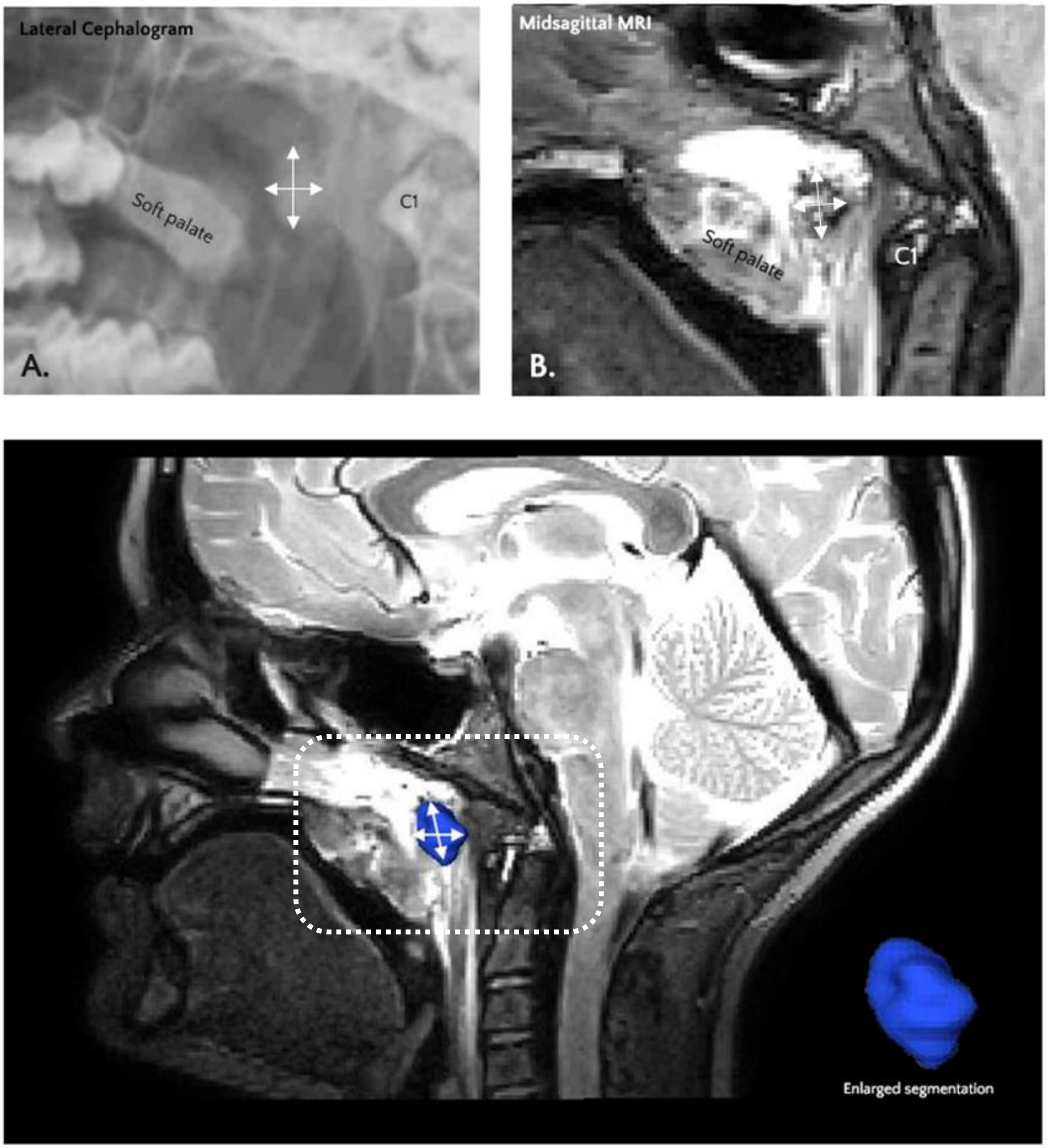


Figure D9.
Example of volumetric pharyngoplasty segmentation (blue) and measures of pharyngoplasty width and height (arrows) on cephalogram (A) and MRI (B). The outlined area in white dashes represents the anatomical area displayed for images A and B.

Significant differences were present between pharyngoplasty width (p = 0.009) between time points #2 and #3 (Table D17). The width of the pharyngoplasty decreased, on average, by 30.36% (~3 mm). Initial post-operative results indicated that pharyngoplasty width ranged from 6.36 – 14.20 mm, with an average width of 9.75 mm. Final width of the pharyngoplasty, based on the anterior projection of the pharyngoplasty tissue from the posterior pharyngeal wall, was 6.97 mm, on average (range, 4.75 – 8.08 mm). Overall, a significant decrease in pharyngoplasty size was noted between the two post-operative imaging time points.

Table D17
Paired Samples T-Tests Pharyngoplasty Width (time points #2 and #3)

	N	Mean (mm)	SD	T	Significance	Result
Pharyngoplasty width at time point #2	7	9.75	2.72	4.130	0.009**	Significant difference
Pharyngoplasty width at time point #3	7	6.79	1.30			

** α = 0.05

Post-operative velopharyngeal portal dimensions. A small decrease in velopharyngeal port dimensions and increased variability was noted in post-operative velar length at time point #3. However, non-significant differences were present for velar length (p = 0.599) pre- and post-operatively (between imaging time points #1 and #3). Pharyngeal depth was noted to decrease post-operatively (19.37 mm vs. 17.81 mm, on average) and differences in pharyngeal depth between time points #1 and #3 were noted to approach significance (p = 0.070). A greater decrease was noted for participants who had a final pharyngoplasty position at or above C1. The average post-operative depth:length ratio did not change substantially when compared to the pre-operative depth:length ratio (0.85 vs 0.83). However, the two participants who demonstrated a post-operative pharyngoplasty location “above” C1 had the smallest pharyngeal depth (ie:

shortest distance between the posterior maxillary point (PMP) and posterior pharyngeal wall). These two participants additionally demonstrated a smaller post-operative depth:length ratios than the group mean (0.76 and 0.79, respectively).

DISCUSSION

Velopharyngeal closure is reported to occur at the level of the palatal plane in children (Satoh et al., 2004; Yoshida, Stella, Ghali, & Epker, 1992) and above the palatal plane after puberty (Kuehn, Folkins, & Cutting, 1982; McKerns & Bzoch, 1970). The palatal plane is often used as a reference line to determine the height of velopharyngeal closure on the posterior pharyngeal wall (Mason, Perry, Riski, & Fang, 2016; Riski et al., 1984; Satoh et al., 2004). Studies have used this plane in reference to the anterior tubercle of C1 to determine how the height of velopharyngeal closure changes across the age span (Mason et al., 2016; Mason, Riski, & Perry, in press; Satoh, Wada, Tachimura, Sakoda, & Shiba, 1999). It has been recommended that secondary surgical management for VPD utilizes the distance between the height of velopharyngeal closure and C1 to determine appropriate intraoperative placement along the posterior pharyngeal wall (Losken et al., 2003; Riski et al., 1984; Riski, Ruff, Georgiade, Barwick, & Edwards, 1992a). Studies show that when secondary surgical placement for the pharyngoplasty is below the level of velopharyngeal closure, poor outcomes occur (Riski et al., 1992b). It is likely that external forces of gravity and scar contracture cause the pharyngoplasty to migrate inferiorly to an unfavorable location compared to the placement during surgery. The amount of inferior displacement, however, is unknown. No studies have examined the initial pharyngoplasty placement and quantified post-operative tissue changes across set time points. This study aimed to examine this critical gap in the literature.

Data from this study evaluated post-operative tissue changes of the pharyngoplasty relative to the nasopharynx and vertebral column, specifically, the anterior tubercle of the first cervical vertebra (C1). Pre- and post-operative cephalometric analyses and post-operative MRI were used to evaluate the location of the pharyngoplasty, visualize the nasopharyngeal airway, and examine the amount and effect of inferior tissue migration on speech outcomes. Data from the present study provides insight into the effect of external forces on the final positioning of the pharyngoplasty.

AIMS I and II

Aims I and II were designed to quantify the pre-operative height of velopharyngeal closure and determine the extent to which the surgeon was able to use pre-operative measures to guide placement of the pharyngoplasty tissue, and to quantify any post-operative tissue change in pharyngoplasty location between two post-operative imaging time points. Pre-operative imaging to quantify the functional height of velopharyngeal closure was utilized to guide surgical placement of the pharyngoplasty. Non-significant differences between the recommended tissue placement, based on the measure of the distance between C1 and the palatal plane, and the initial pharyngoplasty location demonstrate the value of pre-operative imaging for surgical planning.

Significant differences were observed across imaging time points related to pharyngoplasty size and location as well as pre- and post-operative speech data. Notable inferior displacement of the pharyngoplasty tissue resulted in less than favorable speech outcomes, consistent with research by Riski et al. (Riski et al., 1992b; Riski et al., 1992a; Riski et al., 1984). Despite the small number of participants and the heterogeneity in terms of cleft type, the significant differences noted between the two post-operative imaging time points are substantial. The overall amount of inferior tissue displacement ranged from of 0.48 mm – 13.13 mm across participants. Whether or not this displacement resulted in a pharyngoplasty position below C1 was indicative of how high the initial pharyngoplasty tissue was placed. In four of the seven participants, the pharyngoplasty tissue migrated below C1 (and significantly below the height of velopharyngeal closure). The variability observed in the amount of tissue migration demonstrates that post-operative tissue changes are not consistent across individuals; and in most cases, the tissue migrates to an unfavorable positon that is below the palatal plane. Additionally, those with pharyngoplasties located below C1 demonstrated the highest post-operative oral sentence nasometry scores. Thus, results indicate that the final location of the pharyngoplasty influenced speech outcomes. Larger sample sizes are needed to examine this impact and determine if findings are related to additional criteria such as cleft type, race, and age.

All participants demonstrated improvement between pre- and post-operative measures of velopharyngeal function, oral nasometry scores, and perceptual speech ratings, despite tissue migration. However, improvement was variable. Two of the seven participants did not achieve normal resonance post-operatively and demonstrated residual perceptual hypernasality and intermittent audible nasal air emission post-operatively. These two participants also demonstrated the greatest amount of inferior tissue migration and a final pharyngoplasty location below the level of C1. Participants with the least amount of inferior tissue migration (0.48 mm – 2.92 mm of total inferior movement) demonstrated the lowest post-operative oral sentence nasometry scores (9% for both participants) and achieved normal post-operative resonance.

It is well established that pharyngoplasties located below the level of palatal plane are suboptimal and often result in a surgical revision (Riski et al., 1992a). Studies assessing post-operative outcomes have documented low-set pharyngoplasty position, despite attempts to place the pharyngoplasty high in the nasopharynx (Riski et al., 1992a). Attempts to place the pharyngoplasty above the level of closure resulted in an 84-86% success rate (Pryor et al., 2006; Riski et al., 1984). Placement below the attempted level of velopharyngeal closure is commonly related to poor surgical outcomes with failure rates as high as 32.35% (Riski et al., 1984; Riski et al., 1992a).

Riski and colleagues (1992b) evaluated failed pharyngoplasties in 30 patients. Pre-operative cephalograms were used to determine the height of velopharyngeal contact relative to C1 and post-operative cephalograms were taken four months post-operatively to visualize the velopharyngeal port. This allowed for data to be collected at two imaging time points. The first time point provided a recommendation of where the pharyngoplasty should be placed, similar to the current study, and the second time point allowed final pharyngoplasty position to be correlated with speech outcomes. Conclusions from this study indicated that poor post-operative results were secondary to low pharyngoplasty insertion, flap dehiscence, and sphincter flaps that did not approximate the midline. However, there was no indication as to whether the surgeon was able to utilize this recommendation and place the pharyngoplasty at the appropriate level or whether the tissue was placed appropriately and external forces impacted the post-surgical tissue location. The primary limitation of this study (Riski et al., 1992b) was the inability to quantify change over time and determine if the low pharyngoplasty position was a product of low surgical insertion or post-operative tissue changes over time due to external forces.

Within the current study, the use of imaging time point #2 was useful to determine intraoperative tissue insertion site and serve as a comparison for post-operative pharyngoplasty tissue changes. It allowed for the quantification of anatomical and surgical variables immediately post-operatively and provided a comparison for the post-operative anatomy at time point #3. The two post-surgical time points allowed for estimates of the differences between surgical placement and final tissue location. However, volumetric assessment of the nasopharyngeal airway was not possible using the MRI data obtained 1-3 days post-operatively due to the extensive swelling in the tissue. In some cases, the nasopharyngeal airway displayed no visible port or opening in the airway. In all cases, however, the tissue swelling was eliminated at the imaging time point 3. Future studies should consider the use of MRI at all three time points to provide a consistent imaging method and to establish volumetric airway changes across the treatment process. Nasopharyngeal volume likely has a direct impact on speech outcomes (Mason & Perry, 2016) and MRI across each time point can provide a longitudinal assessment of this impact.

Riski et al. (1984) used the post-surgical cephalogram and reported that location of the pharyngoplasty was the strongest predictor of speech outcome compared to age, sex, and velopharyngeal gap size. Although two post-surgical time points were used in the present study, the final location (time point #3, 2-4 months post-operatively) provides the best indication of anatomical contributions from post-surgical migration of the pharyngoplasty to post-operative speech outcome and is consistent with data from previous studies (Riski et al., 1992b; Riski et al., 1992a). It is important to note that all participants displayed a migration of tissue.

Within this sample, those who demonstrated a post-operative pharyngoplasty location greater than three millimeters below C1 also demonstrated higher (worse) oral resonance scores post-operatively. To achieve adequate post-operative velopharyngeal closure, and account for inferior migration, the lateral sphincter flaps should be positioned well above C1. Relative to the data derived from this study, a height of approximately 5mm above the pre-operative height of velopharyngeal closure would have the potential to compensate for the average amount of inferior migration that was observed post-operatively. A limitation to achieving high insertion site, however, is the presences of the adenoid tissue, which is often located near the height of velopharyngeal contact with the posterior pharyngeal wall (Hynes, 1967; Pryor et al., 2006; Riski et al., 1992a). Investigators have suggested partial or complete resection of the adenoid tissue to allow for higher pharyngoplasty inset when needed (Pryor et al., 2006; Riski et al., 1984).

Pharyngoplasty tissue was further analyzed through volumetric segmentation of the pharyngoplasty from MR imaging data. Using computational modeling, Inouye et al. (2015) proposed that midline tissue defects of the palate were the single most significant negative impacting factor for VPD. Similarly, three-dimensional modeling and visualization of the pharyngoplasty volume within this study allowed for analysis of pharyngoplasty integrity at time point #2. Integrity of the pharyngoplasty was noted across the midline in all participants, which likely influenced the improvements observed in post-operative speech outcomes, despite inferior migration. Riski et al. (1992b) reported that inadequate tissue length of the palatopharyngeus muscle can result in dehiscence of the pharyngoplasty post-operatively. This can be related to mechanical and vascular integrity of the longitudinal palatopharyngeus fibers and is a common cause of failed pharyngoplasties.

In cases of failed pharyngoplasties, volumetric segmentation of the pharyngoplasty tissue using MRI creates the ability to visualize sphincter pharyngoplasty tissue integrity three-dimensionally. This visualization has the potential to be utilized for post-operative assessment and future surgical planning when the need for pharyngoplasty revision occurs. Need for revision is reported to occur in 13-33% of cases and is often secondary to obstruction or inadequate pharyngoplasty tissue proportions or location (Kasten et al., 1997; Losken et al., 2003; Witt et al., 1995; Witt, Myckatyn, & Marsh, 1998). Three dimensional visualization of the failed pharyngoplasty has the potential to identify the specific area of tissue dehiscence or the area of obstruction prior to revision with greater detail than lateral radiography and less invasiveness than nasendoscopy.

Pre-operative imaging is an important tool for determining the site of pharyngoplasty tissue insertion along the posterior pharyngeal wall. Using imaging, and taking into account the average amount of inferior tissue displacement observed, can assist in determining appropriate intra-operative tissue insertion height, relative to the first cervical vertebra, to achieve ideal speech outcomes.

AIM III

The third aim of this study was to quantify dimensions of the post-operative nasopharyngeal airway and determine if variables existed that accounted for tissue migration. factors of age, cleft type, and race were not found to be significant predictors of the amount of inferior displacement of the pharyngoplasty. Despite non-significant results, the greatest amount of inferior migration of the pharyngoplasty was observed in the two participants who had diagnoses of bilateral cleft lip and palate. These participants additionally demonstrated the largest pharyngoplasty volume and had a final pharyngoplasty position below the level of C1. Pharyngoplasty volume is likely related to the pre-operative assessment and recommendation based on nasopharyngeal proportions (i.e. patients with a deeper nasopharynx pre-operatively and short velar length are likely to be recommended for a larger pharyngoplasty). The pharyngoplasty size observed in these two participants is consistent with the participant's cleft type, as those with bilateral cleft lip and palate often demonstrate shorter, more scarred palates compared to those with non-cleft VPD or unrepaired submucous cleft palate, due to absence of previous surgical intervention to the palate (Wu, Huang, Huang, & Noordhoff, 1996). Therefore, cleft type may play a role in the determination of the recommended size of pharyngoplasty.

Gravity, as well as internal tissue properties, likely cause the greater volume of tissue associated with pharyngoplasties in more severe clefting to have a larger post-operative migration. Thus, cleft type may indirectly influence the amount of inferior tissue migration observed post-operatively.

Second to pharyngoplasty location, Riski et al. (1992a) also determined that age was an influencing factor of pharyngoplasty success, with younger children demonstrating more favorable outcomes. Further, Mason and colleagues documented age-related changes between the height of velopharyngeal closure and C1 in cleft (Mason et al., in press) and typically developing children (Mason et al., 2016). In older children and children with BCLP, it was noted that the height of velopharyngeal closure was higher above C1 (Mason et al., 2016; Mason et al., in press). The change reported in the height of velopharyngeal closure relative to C1 as children age may impact the functionality of the pharyngoplasty over time secondary to changes in the angulation of the vocal tract relative to the palatal plane as children progress from childhood through puberty (Fitch & Giedd, 1999; Vorperian, Houri K Wang, Shubing Chung, Moo K Schimek, E Michael Durtschi, Reid B Kent, Ray D Ziegert, Andrew J Gentry, Lindell R, 2009). Additionally, after age 13, significant differences become present in the nasopharyngeal area between males and females (Jeans, Fernando, Maw, & Leighton, 1981). Within this sample, all participants fell inside the “child” age range (4-10 years). Therefore, the non-significant influences of age (and sex) on pharyngoplasty tissue migration were expected. A larger sample size may demonstrate clearer age-related trends related to pharyngoplasty migration. However, the variability in the amount of inferior tissue displacement observed across participants within this study sample, despite a similar age grouping, is indicative that additional factors may be contributing to the pharyngoplasty migration.

The prevertebral soft tissue, which can be observed on MRI, consists of the pharyngeal mucosa, muscle, serosa, the prevertebral fascia, and the retropharyngeal areolar space (Rojas et al., 2009). Above this lies the adenoid tissue and pharyngobasilar fascia. Studies have reported that surgical procedures along the pharyngeal wall and prevertebral space cause bleeding and intraoperative soft tissue edema, which can result in post-operative tissue swelling (Frempong-Boadu et al., 2002). The sphincter pharyngoplasty procedure demonstrates similar consequences to the pharyngeal tissue, through dissection and suturing of portions of the tissue within the pharyngeal wall to achieve appropriate tissue placement. Therefore, the presence of post-operative tissue edema is not uncommon and consistent with what was observed within this study sample. However, the pattern of the healing process relative to post-operative decrease in tissue edema and its impact on the pharyngoplasty remains unclear.

The factors of initial pharyngoplasty volume and the amount of post-operative tissue edema were additionally non-significant predictors on the amount of inferior tissue displacement. This may be related to sample size or the variability in patient-specific responses to post-operative wound healing (Werner & Grose, 2003). The internal process of wound healing involves complex interactions at the cellular and biochemical level, which are not easily visualized using MRI. Surgical intervention results in a staged process of tissue healing which includes inflammation, epithelialization, contraction, and remodeling (Stadelmann, Digenis, & Tobin, 1998). The phenomenon of wound contraction serves a role in reducing the size of (and closing) the post-surgical wound. However, critical review of this process by Stadelmann and colleagues (1998) revealed that wound contraction can be indiscriminant and lead to disorganized structural integrity. Race has been reported to be a significant factor in wound healing, especially related to the differentiation of keloid and hypertrophic scars (Muir, 1990;

Niessen, Spauwen, Schalkwijk, & Kon, 1999). However, healing of the mucous membrane appears to be less affected by racial differences than external tissue surfaces (Niessen et al., 1999). Additionally, factors such as gravity and patient-specific responses to surgical intervention, related to internal tissue responses, have been found to impact post-surgical anatomy (Dupps & Wilson, 2006). The process of wound healing on post-operative tissue swelling likely influences overall changes in the pharyngoplasty location and further study is needed within this population.

Final location of the pharyngoplasty was noted to impact the final depth of the velopharyngeal port. Pharyngeal depth was noted to decrease post-operatively (19.37 mm vs. 17.81 mm, on average) and differences in pharyngeal depth between time points #1 and #3 were are likely related to the presence of the pharyngoplasty tissue along the posterior pharyngeal wall in the nasopharyngeal airway. Pharyngeal depth was measured from the posterior maxillary point to the posterior pharyngeal wall. This measure corresponds to the palatal plane and height of velopharyngeal closure. The amount that the effective pharyngeal depth decreased was related to the final location of the pharyngoplasty tissue. A greater decrease was noted for participants who had a final pharyngoplasty position at or above C1. This is due to velopharyngeal closure occurring at the level of the palatal plane and pharyngeal depth being measured at the level of the palatal plane. Therefore, those with pharyngoplasties places “at” or “above” C1 had pharyngoplasty tissue that was placed near the palatal plane, thus creating a smaller velopharyngeal depth and better dimensions for velopharyngeal closure.

Additionally, initial post-operative prevertebral or pharyngeal swelling around the pharyngoplasty was observed in all participants. Volumetric segmentation of the tissue edema demonstrated initial nasopharyngeal obstruction in four of the participants at time point #2.

Within this sample, however, this post-operative tissue edema was not symptomatic for persistent airway obstruction and all inflammation had resolved fully at the post-surgical follow-up appointment. No residual tissue inflammation was noted on the radiographs at imaging time point #3. An overall decrease was noted in the size of the pharyngoplasty between the two post-operative imaging time points. The initial pharyngoplasty width, based on the anterior projection of the pharyngoplasty tissue from the posterior pharyngeal wall, was 9.39 mm, on average, compared to final pharyngoplasty width of 6.97 mm, on average. Riski et al. (1992b) reported similar results with a pharyngoplasty width of 6.22 mm on average and a range of 2 –12 mm from cephalometric analyses of during post-operative speech evaluations, indicating variability in the final pharyngoplasty dimensions.

Migration and contraction of surgical tissue has been discussed in the literature relative to the pharyngeal flap surgery (Blocksma, 1963; Friedman, Haines, Coston, Lett, & Edgerton, 1992; Weber, Chase, & Jobe, 1970). The pharyngeal flap surgical technique differs from the sphincter pharyngoplasty in that it creates a static obturator in the midline of the nasopharynx. This creates a midline, partial obstruction with two lateral ports for breathing and nasal consonants. The pharyngeal flap tissue has been reported to migrate post-operatively as a result of scar contracture between the flap and its location on the pharyngeal wall (Skoog, 1965). Much of the research regarding pharyngeal flap migration was related to contracture of raw tissue surfaces and an inferiorly based pharyngeal flap (Friedman et al., 1992; Sloan, 2000; Yoshida et al., 1992). Intraoperative procedure has been altered for the pharyngeal flap surgery to account for this via the creation of a superiorly based pharyngeal flap, eliminating exposure of raw tissue surfaces, and raising the pharyngeal flap as high as possible along the posterior pharyngeal wall, thus allowing for some contracture and inferior migration of the flap to occur without significant consequences (Weber et al., 1970). A similar strategy can be utilized for the sphincter pharyngoplasty.

To account for post-operative tissue migration and intraoperative tissue edema, measuring the height of velopharyngeal closure pre-operatively, and further inserting the tissue above that level intraoperatively, may account for the inherent tissue migration. This may be beneficial in obtaining a final pharyngoplasty position that is at or above the level of C1 and improve overall speech outcomes. According to Riski et al. (1992a), “no [pharyngoplasty] flaps have ever been found to be too high” during post-operative speech evaluation. Data from this study document a process of quantifying the optimal height of tissue insertion and accounting for post-operative tissue migration during the intraoperative procedure.

Despite this, a number of factors can limit the height of pharyngoplasty placement. Large adenoid pads may be present when attempting to position the palatopharyngeus muscle to form the base of the sphincter pharyngoplasty. Due to the unstable nature of lymph tissue such as the adenoids, in order to achieve high insertion height, incision through the adenoid tissue may be necessary (Riski et al., 1992b; Witt et al., 1995). Sphincter pharyngoplasty tissue inserted at this level and sutured to the pharyngobasilar fascia and superior pharyngeal constrictor muscle allows for some flexibility to counteract post-operative tissue contracture, due to its separation from the cervical vertebrae by connective tissue which forms the retropharyngeal space. In contrast, when the pharyngoplasty is sutured to the prevertebral fascia, the lateral pharyngoplasty tissue can become tethered posteriorly (Riski et al., 1992b). Jackson and Silverton (1977) report the use of a superiorly based incision along the posterior pharyngeal wall to raise lateral sphincter flap insertion higher and this technique has become a common feature of the procedure (Losken et al., 2003; Riski et al., 1992b; Witt et al., 1995).

In addition to the adenoid tissue affecting pharyngoplasty placement, the presence of tonsillar tissue can affect the initial dissection of the palatopharyngeus muscle. Pre-pubescent children have been reported to display larger amounts of tonsillar tissue compared to older children (Jeans et al., 1981). The need to intraoperatively resect this tissue to utilize the palatopharyngeus muscle has been reported to create a larger raw surface area across the tissue which heals through contracture and epithelialization (Riski et al., 1992a). Thus, the processes of initial inflammation and wound healing are associated (Clark, 1998).

Inflammation remains the initial response to surgical intervention and necessary for post-operative healing to occur (Hardy, 1989). Outcomes often depend on the initial impact of surgical intervention and are also influenced by individual genetics (Li et al., 2008). Inflammation was noted in all MRI scans at time point two and limited visualization of specific internal muscular and tissue properties of the pharyngoplasty. While volumetric segmentation of the pharyngoplasty and tissue edema allowed for the visualization and quantification of the surface areas and overall structure, specifics of underlying tissue properties were unable to be obtained.

One of the major challenges of traditional MR imaging is the ability to see deep within tissues with sufficient resolution to provide meaningful information. This was a limiting factor of our MRI scans at time point #2 relative to the amount of post-surgical inflammation that was present. Inflammation increases water content within tissue and thus increases the signal on T2 scans, resulting in bright, white areas on the image. An alternative imaging method such as diffusion tensor magnetic resonance imaging (DTI) has been reported to better characterize properties of skeletal muscle (Longwei, 2012), but has not yet been applied to analysis of the velopharyngeal musculature.

Data derived from post-operative analysis of the pharyngopalsty tissue migration can be incorporated into future patient-specific clinical models with the use of advanced imaging methods. Models that integrate volumetric data, structural anatomy of the nasopharyngeal airway, properties of the pharyngoplasty tissue, and wound healing behavior have the potential to improve clinical outcomes and maximize surgical success.

Limitations

Generalization of data obtained from this preliminary study is constrained by the sample size. A larger sample is needed to draw significant conclusions on pre- and post-operative predictors that may cause pharyngoplasty tissue migration.

Further, three-dimensional analysis of the pharyngoplasty at time point #3 was not able to be completed due to inherent limitations of two-dimensional cephalometric image. Post-operative MRI or DTI across multiple time points would allow greater detail for visualization and analysis of the post-operative tissue properties over time.

Length of follow up time is additionally a limiting factor for understanding long term tissue changes. It remains unknown what changes the pharyngoplasty tissue undergoes after four months post-operatively and if differences across age, cleft type, and race become more apparent. Longitudinal follow up to fully assess the extent of tissue migration and patient-specific variables over time is needed.

Future Directions

Future research is needed to address anatomical and intraoperative factors that may prevent insertion of the pharyngoplasty tissue at heights high enough to compensate for the inferior displacement that is seen post-operatively. This displacement negatively impacts speech outcomes. Riski et al. (1992a) found that pharyngoplasty height was the only statistically significant predictor for speech outcome. Intraoperative procedure may need to additionally account for the average amount of tissue migration. There is a need for identification of patient-specific factors that may impact the amount of tissue migration seen across patients and assessment of tissue migration longitudinally. Advanced imaging modalities beyond traditional MRI, such as diffusion tensor imaging, may expand the anatomic data that can be derived from image scans.

CONCLUSION

Data from this study confirm that inferior tissue displacement of the pharyngoplasty occurs post-operatively. Significant differences were present between the initial site of pharyngoplasty tissue insertion and the final pharyngoplasty location 2-4 months post-operatively. The average inferior movement of pharyngoplasty tissue post-operatively was 6.82 mm, although notable variability was present across participants. Final location of the pharyngoplasty was a significant predictor of speech outcome. Pharyngoplasties located below the level of C1 resulted in poorer perceptual and quantitative measures of speech. Gravity, scar contracture, and patient-specific variables likely interact, impacting final post-operative pharyngoplasty location. Further studies are needed to assess the pattern of tissue migration and determine patient-specific factors that may predict the amount of tissue migration that will occur.

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CHAPTER 7

GENERAL CONCLUSION

The primary cause of failed pharyngoplasty has been identified as insertion of tissue below the point of attempted velopharyngeal contact. Therefore, elevating the height of tissue insertion along the pharynx as high as possible has been advised using the height of velopharyngeal closure and palpation of the first cervical vertebrae (C1) to guide placement. However, studies have failed to define what constitutes surgical placement that is “high enough” for proper velopharyngeal function. Mobility of the pharyngoplasty post-surgically and the effects of scar contracture on final pharyngoplasty position likely contribute to the failure rate that post-operative assessment tends to reveal. No studies have examined the initial pharyngoplasty placement and quantified post-operative tissue changes across set time points.

This study examined the use of pre-operative cephalometric analyses and post-operative MRI to quantify the placement of the pharyngoplasty, visualize the nasopharyngeal airway, and examine the effect of inferior tissue migration on speech outcomes. A series of investigations were designed to explore and validate the use of imaging methodologies to validate study measurements, assess key variables across age and cleft type, and apply 3D modeling and visualization techniques to assess post-surgical tissue changes and speech outcomes following pharyngoplasties.

Study I assessed age-related changes in the vertical distance between the estimated level of velopharyngeal closure in relation to a prominent landmark of the cervical spine: the anterior tubercle of the first cervical vertebra. Results indicated that age was a strong predictor of the vertical distance between the height of velopharyngeal closure relative to C1. Specifically, as age increases, the vertical distance between the palatal plane and C1 becomes greater resulting in the level of velopharyngeal closure being located higher above C1. Results provided insights into the clinical usefulness of using C1 as a surgical landmark for placement of pharyngoplasties in children with repaired cleft palate and persistent hypernasal speech.

Study II determined the impact of age on the height of velopharyngeal closure above C1 in the cleft population. Age and cleft type were significant predictors of the distance between the level of velopharyngeal closure and C1. Those with greater severity of clefting demonstrated larger distances between the level of velopharyngeal closure and C1. Compared to normative data, children with cleft palate have significantly larger distances between the palatal plane and C1.

Study III created 3D volumetric segmentations from magnetic resonance images (MRI) of the nasopharyngeal space and adenoid tissue and to examine the relationship between nasopharyngeal volume, adenoid volume, and linear measures of the velopharyngeal structures, pharynx, and vocal tract in children with and without cleft palate. Significant differences were present in volumetric measures across cleft types. This study highlighted a methodology for the volumetric, three dimensional visualization of nasopharyngeal structures.

Study IV applied the methodologies established in studies I, II, and III to comprehensively examine post-surgical tissue changes relative to the bony cervical landmarks and correlate post-surgical tissue changes to speech outcomes following pharyngoplasties. Data confirmed that inferior tissue displacement of the pharyngoplasty occurs post-operatively. Significant differences were present between the initial site of pharyngoplasty tissue insertion and the final pharyngoplasty location 2-4 months post-operatively. The average inferior movement of pharyngoplasty tissue post-operatively was 6.82 mm, although notable variability was present across participants. Final location of the pharyngoplasty was a significant predictor of speech outcome. Pharyngoplasties located below the level of C1 resulted in poorer perceptual and quantitative measures of speech. Gravity, scar contracture, and patient-specific variables likely interact, impacting final post-operative pharyngoplasty location.

This study provides preliminary data for future, large-scale investigations into the effects of external forces on the final positioning of the pharyngoplasty and for further research into the identification of additional patient-specific factors that may impact post-operative tissue migration. The continued application of advanced imaging methodologies to the study of the velopharyngeal mechanism will directly affect the clinical decision making processes and provide insight for improved surgical outcomes for children with cleft palate and velopharyngeal dysfunction.

APPENDICES

APPENDIX A: PERCEPTUAL SPEECH SAMPLE & RATING SCALES OBTAINED DURING CLINICAL SPEECH EVALUATION

Articulation Screening:
An articulation screening was completed on all patients. This screening assessed the productions of the consonants in English. The following is the articulation screening used:

List of Consonants

POP

P	Papa	B	Baby
T	Top	D	Dada
K	Cat	G	Go
CH	Choo choo	DG	Juice

Hiss

S	Soap	Z	Zebra
F	Foot	V	Valentine
SH	Shoe	ZH	Measure
TH	Thank you	TH	That

Nasal:

M	Mama
N	No
NG	Ring

Low Pressure

L	Lion
W	Water
Y	Yes
R	Red
H	Hello

Following the Articulation Screening, a standard **speech sample** was obtained with IBM Speech Viewer.

	Have child imitate:	*If unable to imitate phrases*:
Use phrases:	Buy baby a bib	baby
	Hi, how are you?	Hi
	Papa popped up	Papa
	Mama made lemon jam	Ma ma ma
	eee , aahh, ooo	oo
	Take teddy a toy	two, tee, tie
	Go get a bigger egg	Go
	Ted has a dog with white feet	
	You shouldn't play in the street	Shhh
	Playing in the snow is fun	
	Suzie saw sally	I see
	Sixty, sixty, six	six

Ask child to tell you their favorite sport/TV show/cookie in order to record a spontaneous speech sample if possible.

Perceptual ratings of speech and resonance were determined through rating speech samples of single words, sentences, and conversational speech sample noted above. Resonance will be categorized as hypernasal, hyponasal, mixed, or normal. Severity ratings were established (ranging from normal to severe on a 6 point scale) based off of the American Cleft Palate/Craniofacial Association's database speech rating scale (1993). Intelligibility was rated on a scale of 1-6 as well. Any compensatory misarticulations were summarized via a check box on the report. Perceptual voice quality was noted as well.
Perceptual Rating Scales used in the evaluation:

Hypernasality (Scale 1-6)
- *Normal*
- *Mild*
- *Mild-Moderate*
- *Moderate*
- *Moderate-Severe*
- *Severe*

Hyponasality (Scale 1-6)
- *Normal*
- *Mild*
- *Mild-Moderate*
- *Moderate*
- *Moderate-Severe*
- *Severe*

Audible Nasal Emission (Scale 1-6)
- *None*
- *Mild*
- *Mild-Moderate*
- *Moderate*
- *Moderate-Severe*
- *Severe*

Velopharyngeal Function (Scale 1-3)
- *Adequate*
- *Marginal*
- *Inadequate*

Oral Pressure (Scale 1-6)
- *Normal*
- *Mildly Reduced*
- *Mild-Moderately Reduced*
- *Moderately Reduced*
- *Moderate-Severely Reduced*
- *Severely Reduced*

Articulation Proficiency (Scale 1-6)
- *Normal*
- *Mild*
- *Mild-Moderate*
- *Moderate*
- *Moderate-Severe*
- *Severe*

Perceptual Voice Quality (Scale 1-6)
- *Normal*
- *Mild*
- *Mild-Moderate*
- *Moderate*
- *Moderate-Severe*
- *Severe*

Intelligibility Overall (Scale 1-6)
- *Normal*
- *Mild*
- *Mild-Moderate*
- *Moderate*
- *Moderate-Severe*
- *Severe*

Compensatory Articulation *(Categorical)*
- *Glottal Stop*
- *Glottal Stop Co-articulation*
- *Pharyngeal Fricative*
- *Pharyngeal Stop*
- *Mid-Dorsum Palatal Stop*
- *Posterior Nasal Fricative*
- *Anterior Nasal Fricative*
- *Other:* ______________

Speech Analysis using Nasometry:

Nasometric measures were gathered using the Kay Elemetrics Nasometer II 6450 (Kay Elemetrics Corp., Lincoln Park, N.J.). Nasometry scores were obtained using standard passages listed below for oral words and sentences, nasal words and sentences, low pressure context phrases, and high pressure context phrases.

Used phrases / words:	mmmmm	mmmm
	Mama made lemon jam	mama
	eee, aahh, ooo	eee, ahh, ooo
	Buy baby a bib	baby
	Hi, how are you	hi
	Papa popped up	papa

Expected range** for normal nasometry scores:

Sustained nasal sound: 95% ± 3

Nasal loaded sentence sample: 61% ± 7

Oral (non-nasal group of sentences): 15.4% ± 6

**Expected scores and norms based on reported data from:

1. Pegoraro-Krook, M.I., Dutka-Souza, J.C., Williams, W.N., Teles Magalhães, L.C., Rossetto, P.C., & Riski, J.E. (2006). Effect of nasal decongestion on nasalance measures. *The Cleft Palate-Craniofacial Journal, 43*(3), 289-294.
2. Fletcher, S.G., Adams, L.E., & McCutcheon, M.J. (1989). Cleft palate speech assessment through oral-nasal acoustic measures. *Communicative Disorders Related to Cleft Lip and Palate. (K. Bzoch, Ed.) Boston: Little, Brown*, 246-257.

APPENDIX B: RIGHT TO REUSE PUBLISHED MANUSCRIPTS IN DISSERTATION

Study I: Journal of Craniofacial Surgery

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Wolters Kluwer

Title: Age-Related Changes Between the Level of Velopharyngeal Closure and the Cervical Spine

Author: Kazlin Mason, Jamie Perry, John Riski, et al

Publication: Journal of Craniofacial Surgery, The

Publisher: Wolters Kluwer Health, Inc.

Date: Aug 16, 0302

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Study II: Cleft Palate Craniofacial Journal

Title:	Age Related Changes between the Height of Velopharyngeal Closure and the Palatal Plane in Subjects with Cleft and Non-Cleft Velopharyngeal Dysfunction
Author(s):	Mason, KN; Perry, JL; Riski, JE
Publication:	Cleft Palate/Craniofacial Journal
Publisher:	SAGE Publishing
Date:	11/12/2017

Study III: Journal of Craniofacial Surgery

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Wolters Kluwer

Title:	Relationship Between Age and Diagnosis on Volumetric and Linear Velopharyngeal Measures in the Cleft and Noncleft Populations
Author:	Kazlin Mason and Jamie Perry
Publication:	Journal of Craniofacial Surgery, The
Publisher:	Wolters Kluwer Health, Inc.
Date:	Aug 16, 0702

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APPENDIX C: INSTUTIONAL AFFILIATION AGREEMENT

Version Date: 5/31/12

Institutional Review Board (IRB)/Independent Ethics Committee (IEC) Authorization Agreement

Name of Institution or Organization Providing IRB Review (Institution/Organization A):
Children's Healthcare of Atlanta

IRB Registration #: 15-075 Federalwide Assurance (FWA) #, if any: Not Applicable

Name of Institution Relying on the Designated IRB (Institution B):
East Carolina University

FWA #: FWA00000658

The Officials signing below agree that East Carolina University may rely on the designated IRB for review and continuing oversight of its human subjects research described below: (*check one*)

( ) This agreement applies to all human subjects research covered by Institution B's FWA.

(X) This agreement is limited to the following specific protocol(s):

Name of Research Project: Examining Insertion Site of the Pharyngoplasty as an Outcome for Success
Name of Principal Investigator: Kazlin Mason
Sponsor or Funding Agency: Cleft Palate Foundation
Award Number, if any: N/A

( ) Other (*describe*):

The review performed by the designated IRB will meet the human subject protection requirements of Institution B's OHRP-approved FWA. The IRB at Institution/Organization A will follow written procedures for reporting its findings and actions to appropriate officials at Institution B. Relevant minutes of IRB meetings will be made available to Institution B upon request. Institution B remains responsible for ensuring compliance with the IRB's determinations and with the Terms of its OHRP-approved FWA. This document must be kept on file by both parties and provided to OHRP upon request.

Signature of Signatory Official (Institution/Organization A):

[signature] Date: 8/7/2015

Print Full Name: PAUL SPEARMAN, MD
Institutional Title: Chief Research Officer

Signature of Signatory Official (Institution B):

[signature] Date: 08/05/2015

Michael R. Van Scott, PhD
Chief Research Officer
East Carolina University

APPENDIX D: INITIAL IRB NOTIFICATION OF APPROVAL

Children's Healthcare of Atlanta
Dedicated to All Better

Date: 07/09/2015

NOTIFICATION OF APPROVAL
Children's Healthcare of Atlanta Institutional Review Board

Study Title: Examining the Insertion Site of Pharyngoplasties as an Outcome for Success
Principal Investigator: John Riski, MD
CHOA IRB#: 15-075
Date IRB Approval Issued: 07/09/2015
Date IRB Approval Expires: 07/08/2016
IRB Review Type: ☐ Full Committee ☒ Expedited
Sites Associated with this IRB Approval:
☐ Children's at Egleston
☒ Children's at Scottish Rite
☐ Children's at Hughes Spaulding
☒ East Carolina University, Department of Communication Sciences and Disorders

Risk Category:
☒ 46.404 OHRP (50.51 FDA)
☐ 46.405 OHRP (50.52 FDA)
☐ 46.406 OHRP (50.53 FDA)
☐ 46.407 OHRP (50.54 FDA)

Children's Healthcare of Atlanta Institutional Review Board approved the above referenced study.

☒ The stamped approved informed consent document for use in this study is attached. Only this original shall be used to make copies for study enrollment. You may not use any informed consent document that does not have this Institutional Review Board's current stamp of approval. The board has determined one parent signature is required.

☐ The requirement for written informed consent is waived for this study. The IRB has determined that all specified criteria described in 45 CFR 46.116 as necessary to obtain a waiver of informed consent.

☐ The requirement for authorization for the release of protected health information for research purposes is waived for this study. The IRB has determined that all specified criteria in 45 CFR 164.512 as necessary to obtain a waiver of HIPAA Authorization.

☐ The requirement for authorization of release of protected health information is partially waived for this study.

☐ This study is open for data analysis only.

While conducting this research, please ensure that the following occur:

- As applicable, informed consent is sought and appropriately documented from each prospective subject or the subject's legally authorized representative before the subject participates in the research.
- IRB approval for continuation of the study is obtained prior to the above referenced expiration date. Failure to obtain approval for continuation prior to the expiration date results in immediate termination of the research at the above referenced study sites.
- Any modification to the study procedures or documents approved by the IRB are submitted to and approved by the IRB prior to implementing the change.
- Serious adverse events reports are reported to the IRB within ten (10) days of knowledge of them.
- Appropriate study records are maintained as mandated by this institution, the sponsoring agency, and the FDA.
- Hospital staff involved with this study are fully informed and trained regarding their involvement with this research or its subjects.

The IRB office may provide a request for continuing renewal at 60 and 30 days prior to the expiration date indicated above. However, it is the Principal Investigator's responsibility to ensure that the continuing renewal materials are submitted in adequate time to allow IRB review and approval prior to the expiration date. Failure to obtain IRB approval for continuation results in immediate termination of the research. In this case, the study may not be re-opened under this CHOA IRB# unless the continuing renewal materials are received within 90 days of the expiration date and approved by the IRB. Otherwise, the study must be submitted as a new protocol and a new CHOA IRB# will be assigned.

As a reminder, in addition to IRB approval, the PI is responsible for obtaining all applicable organizational approvals for the study (Legal, Clinical Engineering, Sourcing, Departmental, etc.).

Sincerely,

Serrena Slaton

Serrena Slaton,
IRB Administrator

Documents Approved:
Protocol - Version date: 06/30/2015
Informed Consent – Version date: 06/30/2015
Assent - Version date: 06/30/2015
HIPAA

APPENDIX E: INFORMED CONSENT/ASSENT DOCUMENTS

Version Date: 06/30/2015

Children's Healthcare of Atlanta
Consent to be in a Research Study

Title: Examining the Insertion Site of Pharyngoplasties as an Outcome for Success

Principle Investigator: Dr. John E. Riski, Ph.D.

Sponsor's Name: The Cleft Palate Foundation

If this form is being read by the parent or legal guardian, the term "you" refers to "your child."

You are being asked to be in a research study. It is entirely your choice. In order to decide whether or not you want to be a part of this study, it is important that you read and understand this form. It is also important that you ask any questions that you may have and that you understand all the information in this form. This process is called "informed consent."

Why is this study being done?
You are being asked to volunteer for a research study because you will be having speech surgery. We would like to learn more about the outcomes of speech surgeries. To do this, we will look at your throat before and after surgery. You have been scheduled to undergo a surgical procedure known as a pharyngoplasty or pharyngeal flap to improve your speech and resonance. Our research has two purposes: 1) to show the use of MRI in watching how you heal from surgery and 2) see if the place in your throat where the pharyngoplasty is attached during surgery changes as you heal.

We plan to enroll 8 participants at Children's Healthcare of Atlanta.

What will happen to you in this study?
As part of the research study only, 2-3 days after your surgery you will be scheduled for an MRI of your head. The MRI will show us what the surgery looks like once your throat has had a few days to heal. During the MRI, you will lay on a flat table and a machine will go around your head making a loud noise. You will wear ear plugs and headphones so the noise won't be too loud. While inside the machine you will have to be really still so that we can get pictures of your head and mouth. If at any point you don't want to keep going or you are scared, all you have to do is tell one of us or push the button while in the scanner.

Information will also be collected from your medical records.

How long will you be in this study?
The time in the MRI scanner will be about 5 minutes per scan and the total visit time is about 60 minutes to allow for preparing the scanner and helping you position yourself in the machine.
Your participation in the study will be complete after you finish your last speech evaluation, which is part of your usual care.

What are the possible risks to being in this study?
You may feel nervous in the MRI machine since the noise will be loud to you. You may ask to stop the MRI at any time you are uncomfortable. If you are unable to complete the MRI, you will not be able to participate in the study but your regular medical care will not change. There are no adverse health risks known to occur from participating in an MRI scan. However, due to the investigational nature of this study there may be risks, discomforts or side effects that are not yet known. The MRI will be looked at by a radiologist. If they see something that they feel requires medical attention, they will refer you to a doctor who can help. There is also a risk of someone outside of the study seeing your private health information. There are procedures in place to protect your information.

What are the possible benefits of being in this study?
Taking part in this research study may not benefit you personally but we may learn new things that may help others in the future. This may help us better support patients with craniofacial anomalies.

Version Date: 06/30/2015

What are the alternatives to being in this study?
Taking part in this study is completely voluntary. The alternative is to not participate in the study and if you choose not to participate in this study your treatment will not be affected. By not participating in the study you would not have an MRI but you would still have a speech evaluation before and after surgery.

What is the cost of being in this study?
This study is funded by the Cleft Palate Foundation. There will be no extra charges to you or your insurance carrier for your participation in this study. You will not be compensated for your time and travel to participate in this study. There will be no charge or billing to your insurance for the MRI.

What if you are injured while in this study?
We will arrange for emergency care or medical treatment if you are injured by this research. No further money has been set aside by Children's Healthcare of Atlanta, Inc. other than what your insurance carrier may provide. For more information about risks or if you believe you have been injured by this research, you should contact Dr. John Riski at 404-785-3688.

What if you have any questions or problems while in this study?
If you have any questions, concerns or complaints about this study call Dr. John Riski at 404-785-3688. If you have any questions, concerns or complaints about your rights as a participant in this study, or would like to obtain information, or offer input, you can call the Children's Healthcare of Atlanta Institutional Review Board (IRB) at (404) 785-7477. The IRB is a committee of people that approves all research in this hospital and follows all the rules and regulations made by government agencies about how research is done.

Who will be able to see your records of study participation?
Your records of participation in this study are not accessible to the general public and every effort will be made to maintain confidentiality. However, all records may be subject to subpoena by a court of law. Information that may be gained from this study will be used only for research and educational purposes. Information may be published in medical journals with permission of the Principal Investigator, but your identity will not be revealed or written in a way that you can be recognized. Additionally, identifying information will be available to people from the Children's Healthcare of Atlanta IRB, the Research Compliance Manager, Office for Human Research Protections, the Sponsor(s), and the Food and Drug Administration. East Carolina University will also be able to see the research data as they are a partner in this study.

We are required to provide study information to the Cleft Palate Foundation (CPF). CPF is the agency sponsoring this study. The information we give to CPF does not identify your child by name or medical record number. If the results of this research are published or presented, information that identifies your child will not be used. No names or other identifying information will be used in any publications or presentations that may result from this study.

What are your rights as a study participant?
Taking part in this study is completely voluntary. You may choose not to take part in this study. If you take part in this study, you may stop being in the study at any time. Your decision to join or not to join the study will not affect your current or future medical care at Children's.

The study doctor may stop you from taking part in this study for any of the following reasons: (1) it would be dangerous for you to continue; (2) you do not follow study procedures; or (3) the study sponsor decides to end the study.

Your signature below indicates that you have read this informed consent form and understand its meaning, you have been given the chance to ask questions and have had those questions answered to your satisfaction, and you voluntarily agree to allow your child to participate in this study and sign this informed consent form. You will be given a copy of the signed informed consent form.

CHOA IRB#: 15-075
Children's IRB Approval: 07/09/2015
Children's IRB Expiration Date: 07/08/2016

APPROVED

Version Date: 06/30/2015

Printed Name of Research Subject	**Age**	**Date of Birth**
Signature of Research Subject (Required unless research subject is under the age of 18 years and assent was not obtained for reason provided below)	**Date**	**Time**
Signature of Research Subject's Parent/Legal Guardian (Required for research subjects under the age of 18 years)	**Date**	**Time**
Signature of Person Obtaining Assent/Consent/Permission	**Date**	**Time**
Signature of Interpreter (if applicable)	**Date**	**Time**

☐ The child is 5 years of age or younger and assent is not required for participation in this research study.
☐ The child is between the ages of 6-10 years old and has been verbally assented to participate in this research study.
☐ In my opinion, the child is not able to assent to participate in this research study for the following reason:

Signature of Person Obtaining Assent/Consent/Permission	**Date**	**Time**

CHOA IRB#: 15-075
Children's IRB Approval: 07/09/2015
Children's IRB Expiration Date: 07/08/2016

APPROVED

Children's Healthcare of Atlanta

Assent to be in a Research Study[1]

Title: Examining the Insertion Site of Pharyngoplasties as an Outcome for Success

Principal Investigator: Dr. John Riski, PhD

Subject age:________years.

Should the assenting child decline participation in this study, they the parent(s), legal guardian(s) cannot force the child to participate.

1.______(< 6years) NO ASSENT REQUIRED

2.______ (ages 6-10) VERBAL ASSENT
The study and the treatment have been explained to this child in an age-appropriate manner. The child has asked questions, verbalizes understanding of the information, and provides verbal assent.

3.______ (ages 11-17) WRITTEN ASSENT See attached Written Assent document.
Once the study and treatment have been explained to the child, he or she should be asked to sign the written assent document. If the process of signing is too intimidating, the consenter may document (here and in the medical record) that the assent as been obtained verbally. It is suggested that the written assent document be read to the child as part of this age-appropriate discussion.

5.______ (any age) UNABLE TO PROVIDE ASSENT
If the child is too immature or otherwise unable to give informed assent, it is the investigator's prerogative to state the following:

In my opinion, this child cannot give informed assent. Reason(s):______________________________

Person Soliciting Assent _______________________ Date ______ Time ______

6. ALL SUBJECTS: Is subject postpubertal? Yes ☐ No ☐ Don't Know ☐

Initial here to indicate you discussed any reproductive risks with the subject ________, or initial here if there are no reproductive risks whatsoever for this study:______

---

[1] For use with prospective subjects ages 6 to 17

CHOA IRB#: 15-075
Children's IRB Approval Date: 07/09/2015
Children's IRB Expiration Date: 07/08/2016
Version Date: 6-30-2015

APPROVED

Written Assent Document

We are asking you to volunteer to be in a medical research study. The study is about using an MRI machine to see how your speech surgery is healing. You will be asked to have an MRI of your head done. It will make a loud noises but it will not hurt. You will be asked to lie on a table and be very still so that the pictures of your head can be taken. You will have to lie still for about five minutes. We are inviting you to be in the study because you are already scheduled to have speech surgery.

You can refuse (say no) to be in this study. Your doctors or your parents cannot make you be in the study if you don't want to be in it.

Your doctor will talk to you about what it means to be in a research study. You should ask your doctor all of the questions you have. You can ask any questions that you have about the study. If you have any questions later, you can call Dr. Riski at 404-785-3688 or ask next time. You can also talk to your parents about the study.

Writing your name on this page means that you agree to be in the study, and you know what will happen to you. You can change your mind and stop being part of this study at any time. Even if you write your name on this paper, you can say no later. All you have to do is tell a parent or the doctor.

________________________________ __________ __________

Participant Date Time

________________________________ __________ __________

Signature of Person Obtaining Assent Date Time

CHOA IRB#: 15-075
Children's IRB Approval Date: 07/09/2015
Children's IRB Expiration Date: 07/08/2016
Version Date: 6-30-2015

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