INVESTIGATION OF THE ANATOMICAL AND PHYSIOLOGICAL CHANGES FOLLOWING THE USE OF A PEDICLED BUCCAL FAT PAD GRAFT DURING PRIMARY PALATOPLASTY

by

Katelyn J. Kotlarek

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Director of Dissertation: Jamie L. Perry, PhD

Major Department: Communication Sciences and Disorders

Children with cleft palate typically undergo primary surgery between 6-12 months of age to close the cleft in the palate and create proper muscle function for elevation and retraction of the velum for speech. About one third of these children require secondary surgical intervention to eliminate hypernasal speech due to velopharyngeal dysfunction (VPD). However, it is currently inconclusive what factors influence the likelihood of developing VPD.

A series of investigations were designed and implemented to explore post-surgical anatomical and physiological changes to the velopharynx. Study I identified differences in the levator veli palatini (levator) muscle of adults with cleft and non-cleft anatomy. Study II determined if there were any positional differences or asymmetry or within the velopharynx or levator muscle between children without cleft palate, those with cleft palate with complete velopharyngeal closure, and those with cleft palate and VPD. Lastly, study III sought to compare velopharyngeal anatomy and physiology among children with cleft palate who have undergone primary palatoplasty with buccal fat pad (BFP) graft placement to those who have undergone more traditional surgical methods as well as a normative control group.

Data from study III, the final study, confirmed that those children who underwent BFP graft placement have a post-operative mechanism that is much different than that of children with traditionally repaired cleft palate as well as a normative group of peers. Significant differences were present for effective velar length, velar thickness, and percentage of fat tissue within the palate. This study confirms that the BFP material is present within the palate up to five years post-surgery and may create more favorable dimensions for velopharyngeal closure.

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by

Katelyn J. Kotlarek

APPROVED BY:

DIRECTOR OF
DISSERTATION: ______________________________
(Jamie L. Perry, PhD)

COMMITTEE MEMBER: ______________________________
(Charles Ellis, PhD)

COMMITTEE MEMBER: ______________________________
(Xiangming Fang, PhD)

CHAIR OF THE DEPARTMENT OF
COMMUNICATION SCIENCES AND DISORDERS: ______________________________
(Jamie L. Perry, PhD)

DEAN OF THE GRADUATE SCHOOL: ______________________________
(Paul J. Gemperline, PhD)

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LIST OF ABBREVIATIONS

VPD	Velopharyngeal dysfunction	1
BFP	Buccal fat pad	2
Levator	Levator veli palatini	3
MRI	Magnetic resonance imaging	3
VPC	Velopharyngeal closure	4
VPI	Velopharyngeal insufficiency	4
3D	Three-dimensional	4
2D	Two-dimensional	4
VP	Velopharyngeal	4
CN	Cranial nerve	29
A-P	Anterior to posterior (orientation)	60
M-L	Medial to lateral (orientation)	60
S-I	Superior to inferior (orientation)	60
DICOM	Digital Imaging and Communication in Medicine	81
PI	Principal investigator	103

CHAPTER 1

INTRODUCTION

Cleft lip and/or palate is the most common birth defect in the United States affecting one in 600 births (Cleft Palate Foundation, 2014). A cleft palate is a congenital defect that results in a hole in the roof of the mouth. Having a cleft impacts every aspect of a child's life, including physical, communication, social, and emotional components. Cleft palate can cause a multitude of issues, including feeding disorders, speech impairment, conductive hearing loss, psychosocial issues, various dental anomalies, and obstructive sleep apnea (Cleft Palate Foundation, 2014). Children typically undergo surgery between 6-12 months of age to close the cleft in the palate and create proper muscle function for elevation and retraction of the soft palate against the posterior pharyngeal wall during speech.

Even after cleft palate surgery, many children continue to have nasal sounding speech (Kummer, 2008). Velopharyngeal dysfunction (VPD) refers to a condition where the velopharyngeal portal does not close consistently and/or completely during the production of oral phonemes, which manifests as hypernasality, obligatory nasal air emission, and/or weak pressure consonants during speech production (Kummer, 2008). It is estimated that 25-37% of children with a repaired cleft palate need a second surgery to eliminate hypernasal speech (Bicknell, McFadden, & Curran, 2002; Lithovius, Ylikontiola, & Sandor, 2014). Around 3-4 years of age, as children acquire more connected speech, the presence of hypernasality becomes evident in this percentage of the population that may require further surgical intervention to address structural causes of hypernasality. It is currently unclear what predisposes an individual with repaired cleft palate to develop VPD. Studies have shown that those with VPD after primary palatoplasty tend to have a shorter velum, greater velopharyngeal depth, greater depth:length ratio, and reduced velar stretch (D'Antonio et al., 2000; Randall et al., 2000; Satoh et al., 2005; Tian et al., 2010b). However, no studies have conclusively determined whether these differences observed in cleft anatomy are related to VPD.

The buccal fat pad (BFP) is a bilateral, encapsulated mass located between the buccinator and masseter muscles of the cheek. The BFP graft (or flap) is a well-documented technique for closure of oral defects, including literature pertaining specifically to the repair of cleft palate fistulae (Ashtani et al., 2011; Egyedi, 1977; Grobe et al., 2011; Habib & Medra, 2016; Hanazawa et al., 1995; Jain et al., 2012). Literature has presented the utilization of the BFP in primary palatoplasty with satisfactory surgical results based on oral inspection, showing increased velar length, decreased midline tension, and no fistulae (Kim, 2001; Levi, Kasten, & Buchman, 2009; Pappachan & Vasant, 2008; Pinto & Debnath, 2007; Yamaguchi et al., 2016; Zhang, et al. 2010). Because this literature base relies on oral inspection without a comparison group and does not include quantitative data, it remains unclear how the use of adipose tissue within the palate alters the velopharyngeal anatomy and how such alterations ultimately impact speech. The purpose this study is to inform our understanding of the structural changes in the velum and to describe the functional effects to the velopharyngeal portal following the use of pedicled BFP graft used during primary cleft palate repair.

To explore and validate our measurement approach in assessing post-surgical anatomical changes, a series of investigations were designed and implemented to (1) examine the differences in cleft and non-cleft anatomy among adults (Study I) and children (Study II) who received traditional cleft palate surgical approaches and (2) to then examine how the use of BFP grafting impacts the velopharyngeal anatomy and function among children with cleft palate (Study III). These series of investigations are further described below:

Study I: Do differences exist in the levator veli palatini muscle morphology between cleft and non-cleft adults?

Kotlarek, K. J., Perry, J. L., & Fang, X. (2017). Morphology of the levator veli palatini muscle in adults with repaired cleft palate. *Journal of Craniofacial Surgery, 28*(3), 833-837.

The purpose of this study was to examine differences in levator veli palatini (levator) morphology between adults with repaired cleft palate and adults with non-cleft anatomy. Fifteen adult participants (10 with non-cleft anatomy, five with repaired cleft palate) completed three-dimensional static magnetic resonance imaging (MRI). Image analyses included measures of total muscle volume and the circumference and diameter at six points along the length of the muscle. Differences between groups were analyzed using independent sample Mann-Whitney U-Tests ($\alpha = 0.05$). Significant differences between groups were noted for measures of muscle volume, circumference at the origin and insertion, anterior-posterior diameter at the origin and midline, and superior-inferior diameter at the point of insertion into the velum and midline. Differences in measures at other points along the levator muscle belly were not statistically significant. Limited sample size and gender differences may have impacted statistical findings. Overall, the levator muscle in adults with repaired cleft palate is significantly different than that of adults with non-cleft anatomy. This study demonstrates the successful implementation of a method for three-dimensional analysis of velopharyngeal musculature with potential clinical utility given continued technological advancements in MRI. Continued evaluation of pre- and post-surgical anatomy and short- and long-term outcomes may contribute to a better understanding of the effects of various types of palatoplasties on levator structure, which is important to velopharyngeal function for speech.

Study II: Do differences exist in the symmetry and positioning of the levator veli palatini muscle in children with and without velopharyngeal insufficiency?

Kotlarek, K. J., Pelland, C., Blemker, S. S., Jaskolka, M. S., Fang, X., & Perry, J. L. Asymmetry and Positioning of the Levator Veli Palatini Muscle in Children with Repaired Cleft Palate. *In preparation*.

The purpose of this study was to examine the differences in velopharyngeal dimensions as well as levator muscle morphology and symmetry of children with repaired cleft palate with VPD, children with repaired cleft palate with complete velopharyngeal closure (VPC), and children with non-cleft anatomy. Fifteen English-speaking children ranging in age from 4-8 years were recruited for this study. Ten of the participants had a history of repaired cleft palate, half with documented velopharyngeal insufficiency (VPI) and the other half with adequate velopharyngeal closure (VPC). Five participants with non-cleft anatomy were matched for age from a normative database. In addition to previously-reported 2D and 3D variables, differences between the left and right sides of the levator were calculated as separate variables for angle of origin, muscle length, and muscle thickness at six predefined points along the length of the muscle. Using multiple Kruskal-Wallis H tests, median values were statistically significantly different between groups for sagittal angle and effective VP ratio, average extravelar length, thickness at midline, and thickness between the left and right levator muscle bundles at the point of insertion into the velum. Participants with repaired cleft palate and VPD displayed the greatest degree of asymmetry. Continued evaluation of post-surgical anatomy and short- and long-term outcomes may contribute to a better understanding of surgical impact on velopharyngeal morphology.

Study III: Does a pedicled BFP graft placement at the palatine aponeurosis during the time of primary palatoplasty create more favorable velopharyngeal dimensions for velopharyngeal function during speech?

The overarching aim of this study was to inform our understanding of the structural changes in the velum and to describe the functional effects to the velopharyngeal portal caused by a pedicled BFP graft used during primary cleft palate repair. More specifically, we compared this procedure to non-pedicled BFP graft surgical cases and normal anatomy to determine if the use of a pedicled BFP graft during primary palate repair creates a more favorable velopharyngeal system for speech production compared to traditional methods. Studies have described the use of the pedicled BFP graft at the time of primary palate repair, hypothesizing that this technique results in an increase in vascularized tissue within an otherwise denuded space at the posterior hard palate. In such, it is expected that this increase in volume and vascularity provided by the pedicled BFP graft would prevent wound contracture, thus maintaining a longer velum and optimizing maxillary growth. There have also been claims that this technique results in increased velar length (Pappachan & Vasant, 2008), which is considered by some (D'Antonio et al., 2000; Nakamura et al., 2003; Randall et al., 2000; Satoh et al., 2005) to be a predictor of successful speech outcomes and normal velopharyngeal function for speech. Up to this point, these hypotheses regarding velar lengthening, decrease in velar scar composition, and thus improved velar function have not been systematically examined and compared to children with cleft palate not receiving a pedicled BFP graft nor children without cleft palate. Prior to this study, the effect the pedicled BFP graft has on palatal and velopharyngeal anatomy was unknown. Furthermore, to the best of our knowledge, no studies to date have applied MRI methods to examine the tissue composition and structural and functional changes as a result of the pedicled BFP graft. The purpose of this study was to use MRI to examine the surgical impact of the pedicled BFP graft on velar composition and velopharyngeal anatomy after it is placed at the palatine aponeurosis at the time of primary palate repair. These findings were compared to aged-matched controls with normal velopharyngeal anatomy and children with repaired cleft palate who have received traditional surgical procedures. The long-term goal of this study is to improve our understanding of the application of a pedicled BFP graft in cleft palate repair and evaluate the outcomes compared to those not receiving a pedicled BFP graft and to normative data, which may allow the acquisition of new knowledge to treat and help prevent additional surgeries for individuals born with cleft palate. The specific study aims are as follows:

Aim I: To define anatomic velopharyngeal changes related to the use of a pedicled BFP graft at the time of primary palatoplasty

Hypothesis I. Children with a pedicled BFP graft display an increased effective velar length, velar thickness, and posterior placement of the levator muscle sling post-surgically compared to those without a pedicled BFP graft and measures are more similar to that of non-cleft controls.

Rationale. Levator and velopharyngeal dimensions have an impact on adequate velopharyngeal closure necessary for proper speech. Studies have hypothesized that the use of a pedicled BFP graft during primary palatoplasty increases velar length by creating vascularized tissue at the junction between the hard and soft palate and thus reducing velar scar tissue (Levi et al., 2009; Pappachan & Vasant, 2008). However, these hypotheses have not been systematically investigated. Through this aim, the effect of surgery on palatal measures using a pedicled BFP graft during primary palatoplasty with be quantified and compared to children surgically treated without the use of a pedicled BFP graft. Specifically, two-dimensional measures of velar length, velar thickness, and posterior placement of the levator sling within the velum were determined.

Aim II: To define tissue type within the velum related to the use of a pedicled BFP graft at the time of primary palatoplasty

Hypothesis IIa. Children with a pedicled BFP graft display an increased percentage of fat tissue post-surgically compared to those without a pedicled BFP graft and non-cleft controls.

Hypothesis IIb. Children with a pedicled BFP graft display an increased percentage of muscle tissue post-surgically compared to those without a pedicled BFP graft and are more similar to that of non-cleft controls.

Rationale. Levi and colleagues (2009) proposed the use of a pedicled BFP graft resulted in an increase in vascularized tissue posterior to the hard palate region and a decrease in velar scar accumulation. Based on visual inspection, clinical reports have hypothesized that this tissue epithelializes within the oral cavity when utilized to treat oral defects, including when this tissue is used during primary palatoplasty (Kim, 2001; Levi, Kasten, & Buchman, 2009). Traditionally, histological analyses on the velum have been limited to post-mortem studies of cadaveric material. Bae, Kuehn, and Sutton (2016) demonstrated a method to categorize tissue type within the velum of living individuals using high-resolution, T2-weighted MRI. Hypothesis IIa and IIb employed methods similar to those utilized by Bae, Kuehn, and Sutton (2016) to determine the tissue composition of the velum in each of the three participant groups by segmenting slices of the velum based on tissue type. In addition to identifying velar muscle and other tissue, fat was also identified within the participants.

Aim III: To determine if the use of a pedicled BFP graft at the time of primary palatoplasty results in greater velar stretch during speech compared to children with cleft palate without a pedicled BFP graft.

Hypothesis III. Child participants treated surgically with a pedicled BFP graft at the time of primary palatoplasty demonstrate a greater velar stretch during speech compared to those not receiving a pedicled BFP graft and more similar to children without a history of cleft palate.

Rationale. Levi and colleagues (2009) proposed the use of a pedicled BFP graft resulted in an increase in vascularized tissue posterior to the hard palate region and a decrease in velar scar accumulation. Velar stretch is the ability of the velum to increase in intrinsic length from rest to elevation for velopharyngeal closure (Pruzansky & Mason, 1969). Velar stretch is dependent on available muscle mass, range/speed of movement, and synergy of other muscles (Pruzansky & Mason, 1969). Limited velar stretch during speech is most likely due to resistance and rigidity of velar scars (Tian et al., 2010b), and therefore, reducing scar tissue should have a direct impact in improving velopharyngeal function for speech. Individuals with repaired cleft palate were found to have decreased levator muscle volume compared to those without cleft palate (Kotlarek et al., 2017). Tian and colleagues (2010b) found velar stretch was the only variable related to motion that differentiated between participants with VPD (resulting in hypernasal speech) and those with cleft palate who had complete velopharyngeal closure and normal speech. Through this aim, we examined if the use of a pedicled BFP graft results in improved velar stretch during speech.

Products of Dissertation

Publications

Kotlarek, K. J., Blemker, S. S., Fang, X., Jaskolka, M. S., Ellis, C., Sutton, B. P., & Perry, J. L. Anatomical and physiological changes following the use of a pedicled buccal fat pad graft during primary palatoplasty. *In preparation*.

Kotlarek, K. J., Blemker, S. S., Fang, X., Jaskolka, M. S., Ellis, C., Sutton, B. P., & Perry, J. L. Cross-sectional tissue changes in the velum following the use of a pedicled buccal fat pad graft during primary palatoplasty. *In preparation.*

Kotlarek, K. J., Pelland, C., Blemker, S. S., Jaskolka, M. S., Fang, X., & Perry, J. L. Asymmetry and Positioning of the Levator Veli Palatini Muscle in Children with Repaired Cleft Palate. *In preparation*.

Kotlarek, K. J., & Perry, J. L. (2018). Velopharyngeal anatomy and physiology. *Perspectives in Craniofacial and Velopharyngeal Dysfunction, 3*(1), 13-23.

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Kotlarek, K. J., Perry, J. L., & Jaskolka, M. (2018, September). MRI findings before and after primary and secondary surgery in individuals with cleft palate. Poster session at the 2nd International Symposium on Velopharyngeal Dysfunction, Columbus, OH.

Kotlarek, K. J., & Perry, J. L. (2018, April) Three-dimensional comparison of the levator veli palatini muscle between children with and without cleft palate. Poster presentation at the East Carolina University College of Allied Health Sciences Research Day, Greenville, NC.

Kotlarek, K. J., Blemker, S., & Perry, J. L. (2018, April). Comparison of velopharyngeal dimensions between children with and without repaired cleft palate. Platform paper presented at the American Cleft Palate-Craniofacial Association 75th Annual Meeting, Pittsburgh, PA.

Kotlarek, K. J., Hughes, A. J., & Perry, J. L. (2017, November) Three-dimensional comparison of the levator veli palatini muscle between children with and without cleft palate. Poster session at the American Speech-Language-Hearing Association Convention, Los Angeles, CA.

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CHAPTER 2

LITERATURE REVIEW

This review of the current literature presents relevant information associated with the anatomy and physiology of the velopharyngeal mechanism as it relates to cleft palate. Surgical approaches regarding the primary closure of the cleft palate are discussed, as well as indications for secondary surgical intervention for velopharyngeal dysfunction (VPD). Current research related to assessment through imaging modalities and computational modeling is summarized.

Incidence of Cleft Palate

Orofacial clefting refers to two distinct defects: cleft palate (without cleft lip) and cleft lip with or without cleft palate. Orofacial clefting, in the absence of other birth defects, is the most common form of birth defect in the United States (Parker et al., 2010). The Centers for Disease Control recently estimated that 2,650 babies are born with a cleft palate and 4,440 babies are born with a cleft lip with or without a cleft palate each year in the United States (Parker et al., 2010). Clefting can also occur in conjunction with over 400 known syndromes (Winter & Baraitser, 1987). Cleft palate and other velopharyngeal anomalies can result in VPD which causes issues with speech and resonance.

Velopharyngeal Anatomy and Physiology[1]

The velopharyngeal mechanism is a three-dimensional, dynamic system that provides separation between the oral and nasal cavities (Jones, 2012). The harmonious physiologic relationship of the velopharyngeal musculature creates adequate opening and closing of the velopharyngeal port during speech production and swallowing. When the velopharyngeal

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[1] **Kotlarek, K.J.**, & Perry, J.L. (2018). Velopharyngeal anatomy and physiology. *Perspectives in Craniofacial and Velopharyngeal Dysfunction, 3*(1), 13-23.

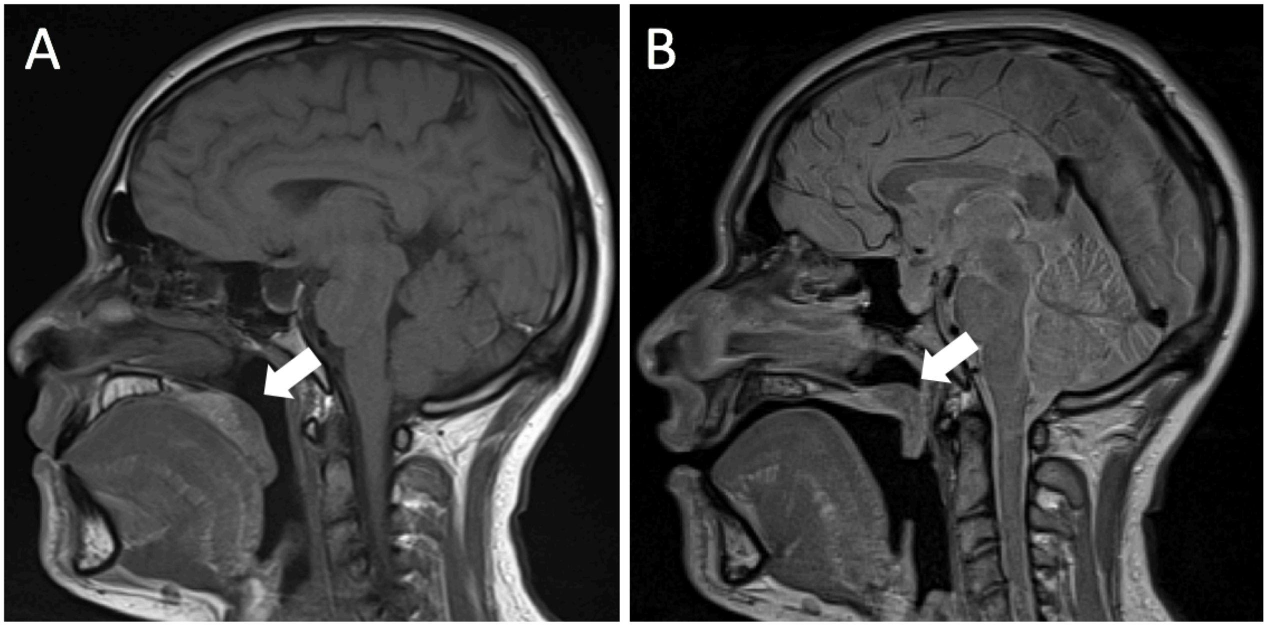
mechanism does not adequately close to separate the nasal cavity from the oral cavity during oral speech, velopharyngeal dysfunction results and is perceived as hypernasality and/or obligatory nasal air emission.

Form. The velopharyngeal mechanism is a muscular valve that extends from the posterior margin of the bony hard palate to the posterior pharyngeal wall (Moon & Kuehn, 2004). It is bounded anteriorly by the velum (or soft palate), laterally by the lateral pharyngeal walls, and posteriorly by the posterior pharyngeal wall. The velum extends posteriorly from the horizontal plate of the palatine bone (hard palate) via the palatine aponeurosis. The three-dimensional space posterior to the relaxed velum is known as the “velopharyngeal port.”

Histologic studies have described the velum to be comprised of tendinous, muscular, adipose, connective, and glandular tissue (Ettema & Kuehn, 1994; Kuehn & Kahane, 1990). The palatine aponeurosis is a tough, tendinous sheath, directly posterior to the posterior margin of the hard palate. The palatine aponeurosis transmits muscle forces and acts as an intermediate area between a highly movable (velum) and immovable (hard palate) structure while providing support and stiffness to the velum. The anterior two-thirds of the velum is rather consistent in composition and organization; however, the posterior one-third of the velum shows greater variability across individuals, which demonstrates the importance of the anterior portion to the functional requirements of velopharyngeal closure (Kuehn & Moon, 2005). Uvulopalatoplasty (surgical removal of the uvula) is performed to treat mild obstructive sleep apnea and has been shown to have no impact on speech, thus providing further evidence of the insignificance of this region for speech (Walker & Gopalsami, 1996). No muscle fibers attach to the posterior margin of the hard palate in the normal velum, which allows for an unrestrained backward movement of the velum during velopharyngeal closure (Azzam & Kuehn, 1977; Dickson, 1975; Kuehn & Moon, 2005).

Function. The primary function of the velopharyngeal mechanism is to form a seal between the nasal and oral cavities to produce normal resonance and create a positive pressure during swallowing. Velopharyngeal closure allows for the buildup of air pressure within the oral cavity that is completely or partially obstructed by the lips, tongue, and teeth and subsequently released to produce oral consonants such as plosives, fricatives, and affricates. Figure 1 shows a magnetic resonance image from the midsagittal plane at rest (A) and during sustained /i/ phonation (B). Velopharyngeal closure (Figure 1, B) is required to swallow and accurately produce oral phonemes, that is, all phonemes except /m/, /n/, and /η/, which are produced with an open velopharyngeal port. The velar knee (Figure 1, arrow) elevates superiorly and posteriorly to contact the posterior pharyngeal wall during velopharyngeal closure. Velar stretch, or the ability of the velum to increase in intrinsic length from rest to elevation, causes the velum to be longer during elevation than rest and is a significant contributor to adequate velopharyngeal closure (Pruzansky & Mason, 1969).

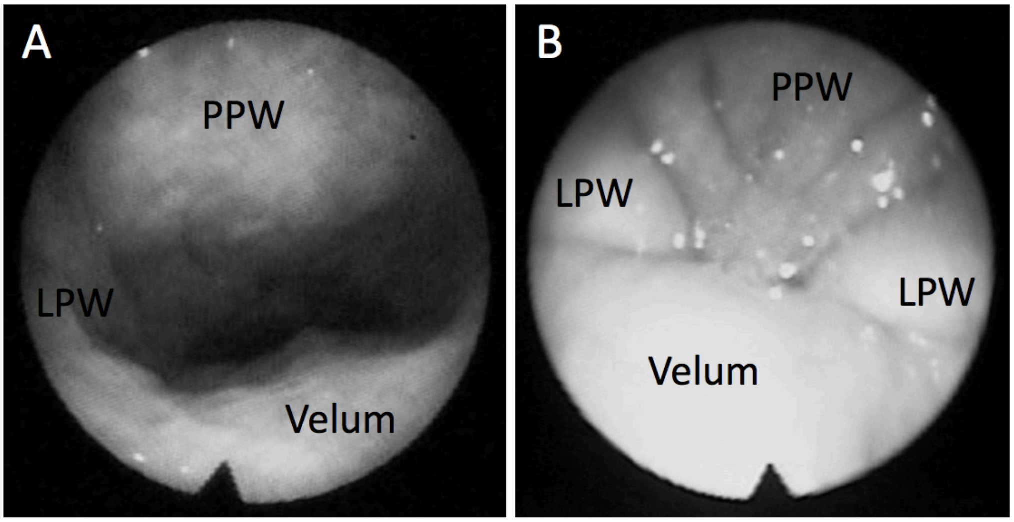
Figure 1. A midsagittal MRI showing the velum at rest (A) and elevated against the posterior pharyngeal wall for sustained production of /i/ (B). White arrows point to the velum at the velar knee in either image.



Velopharyngeal closure is also achieved during the latter part of the oral stage of swallowing to prevent the bolus from entering the nasopharynx and maintain positive pressure on the bolus as it moves caudally through the pharynx (Groher & Crary, 2010). Although children with repaired cleft palate rarely have dysphagia after palate repair (Logemann, 1998), 25-37% have been shown to have speech deficits (Bicknell, McFadden, & Curran, 2002; Lithovius, Ylikontiola, & Sandor, 2014); therefore, the remainder of this article will focus on velopharyngeal function as it relates to speech.

Velopharyngeal closure patterns. There are four movement patterns that describe velopharyngeal closure: Sagittal, coronal, circular with a Passavant's ridge, and circular without a Passavant's ridge (Finkelstein et al., 1993; Skolnik, Shprintzen, McCall, & Rakoff, 1975). An open (A) and closed (B) velopharyngeal port can be visualized while viewing superiorly via nasendoscopy in Figure 2. In the *sagittal* closure pattern, the primary movement is completed by the lateral pharyngeal walls as they displace medially. The velum and posterior pharyngeal wall typically show minimal to no movement toward closure, and the lateral pharyngeal walls far outweigh their contribution. In the *coronal* closure pattern, the velum moves posteriorly to meet the posterior pharyngeal wall. The lateral and posterior pharyngeal walls show very minimal or no movement at all. In the *circular* closure pattern, the velum and lateral pharyngeal walls approximate with equal contribution to achieve velopharyngeal closure. During the circular closure pattern, a bulge in the posterior pharyngeal wall, known as the Passavant's ridge, can be present in some speakers. If the Passavant's ridge is at the level of velopharyngeal closure, it can contribute to velopharyngeal closure. However, Kummer (2008) emphasized it is highly unlikely that the Passavant's ridge appears in an appropriate position to support velopharyngeal closure.

Figure 2. The velopharyngeal port is shown via nasendoscopy at rest (A) and during oral speech production with a circular closure pattern (B).



Croft, Sprintzen, and Rakoff (1981) reported the distribution of these patterns across populations with normal and abnormal velopharyngeal anatomy. Both groups exhibited a similar distribution of closure patterns; the coronal closure pattern was the most common among both groups. Velopharyngeal closure is often observed in conjunction with an enlarged adenoid pad, which is typically seen in children before developmental involution of the adenoids during adolescence (Kummer, 2008; Subtelny & Koepp-Baker, 1956). The velum normally adapts to achieve adequate velopharyngeal closure as the adenoids involute during adolescence, but occasionally the velum may not have sufficient size or mobility to contact the smaller adenoid pad (Perry & Kuehn, 2016). Velopharyngeal closure patterns have also been noted to change across the lifespan, specifically at the onset of puberty and with adenoid involution (Siegel-Sadewitz & Shprintzen, 1986). However, this research has also shown that individuals with cleft palate are less likely to change their closure pattern compared those with non-cleft anatomy, demonstrating a dynamic system that is less adaptable in those with cleft palate (Siegel-Sadewitz & Shprintzen, 1986).

Musculature of the velopharynx

Levator veli palatini. The levator veli palatini muscle originates at the anterior petrous portion of the temporal bone at the base of the skull and courses anteriorly, medially, and inferiorly to the point of insertion within the intermediate 40% of the velum (Boorman & Sommerlad, 1985). The muscle, in its entirety from origin to insertion, can be seen in Figure 3 (smaller image in the left corner demonstrates the plane from which the main image is obtained). The right bundle of the levator veli palatini (labeled LVP) muscle is braced from origin to insertion. The arrow is pointing to the musculus uvulae (labeled MU), which is covered later in this article. The levator veli palatini can also be visualized in Figure 4 (A). The muscle may also have attachments to the junction of the cartilaginous and bony parts of the Eustachian tube (Huang, Lee, & Rajendran, 1998). The levator veli palatini muscle fibers fan out as the muscle enters the body of the velum, and there is no midline separation between the two muscle bundles (Kuehn & Moon, 2005; Perry, Kuehn, & Sutton, 2013). The two points of insertion create a muscular sling with interdigitated muscle fibers at the velar midline.

The levator veli palatini muscle is the primary muscle responsible for velar elevation and retraction. Upon contraction, the levator veli palatini muscle sling elevates and retracts the velum to make contact with the posterior pharyngeal wall.

Musculus uvulae. The musculus uvulae originates from the palatine aponeurosis at approximately one-fourth the length of the velum and courses posteriorly along the midline of the velum. The musculus uvulae is positioned superior to the levator veli palatini muscular sling (Figure 3, arrow) while its fibers course perpendicularly to the levator veli palatini within the body of the velum. The muscle can be visualized in Figure 4 (labeled “B”). The musculus uvulae presents as a bilateral muscle in some individuals and a single muscle bundle in others; however, the bilateral or unilateral nature of the muscle poses no functional significance, as it is a midline muscle (Kuehn & Moon, 2005).

The musculus uvulae acts to add bulk to the velum at the velar eminence and creates a complete seal between the velum and posterior pharyngeal wall (Kuehn, Folkins, & Cutting, 1982). It has been proposed that, like the upper layer of a double-layer beam, contraction of the musculus uvulae causes the velum (the beam) to curl upward and arch posteriorly against the posterior pharyngeal wall to create a firm velopharyngeal seal (Kuehn, Folkins & Cutting, 1982). Inouye, Lin, Perry, and Blemker (2016) used computational modeling to demonstrate the importance of the musculus uvulae in providing adequate midline mass to the velum, producing a convex nasal surface to promote optimal closure force during velopharyngeal closure.

Figure 3. A midsagittal MRI (lower left) showing the velum at rest with the oblique-coronal plane drawn as a white diagonal line. An oblique-coronal image, taken from the plane of the levator veli palatini muscle, is shown at rest. The right bundle of the levator veli palatini muscle (LVP) is braced from origin to insertion. The arrow is pointing to the musculus uvulae (MU).

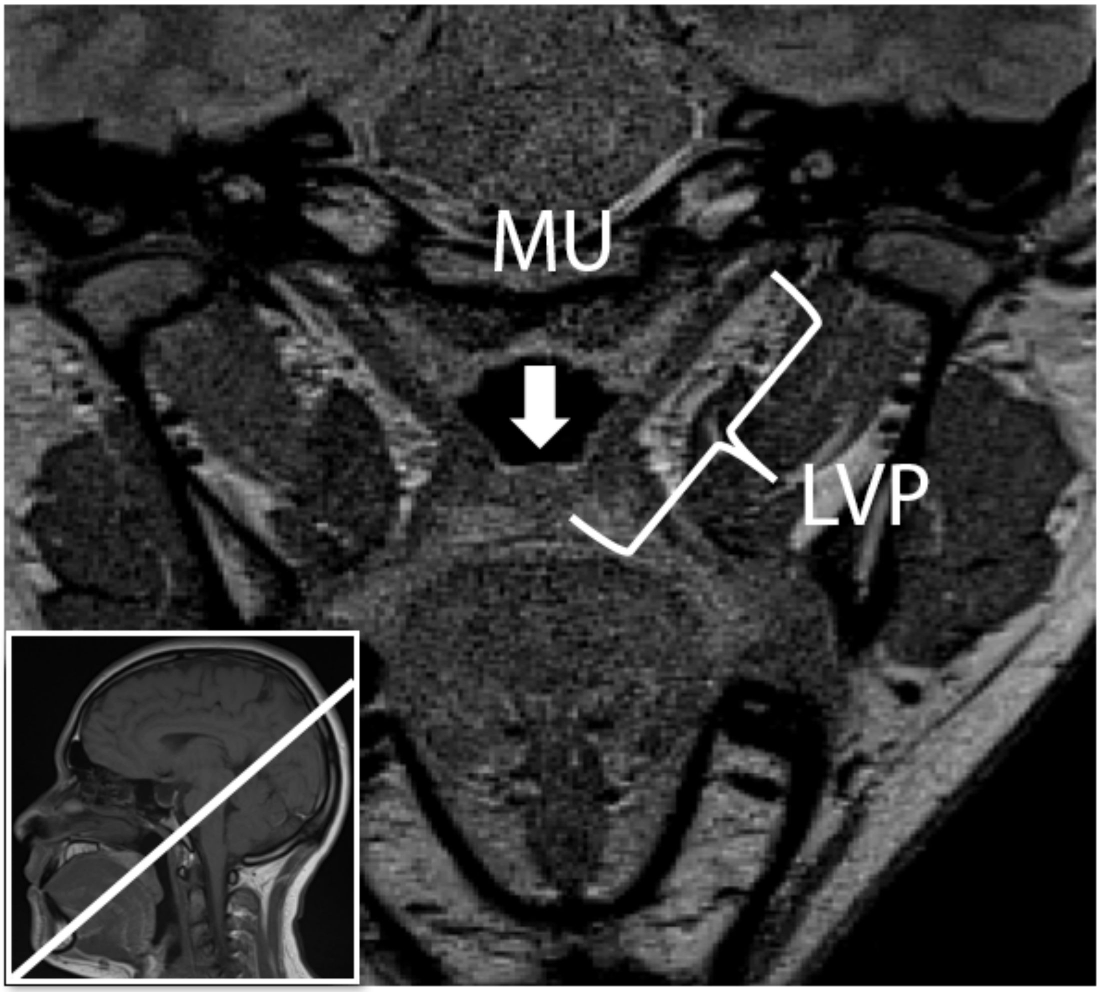
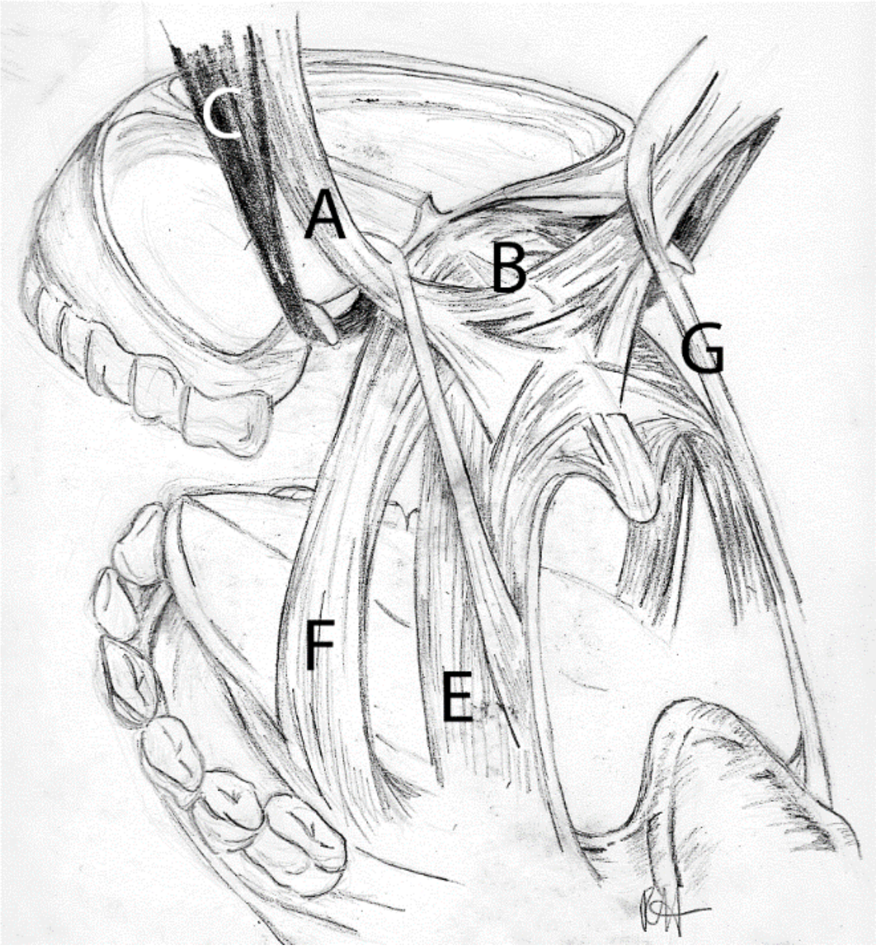


Figure 4. A three-quarter view of the velopharyngeal musculature is shown. Note the following muscles: (A) levator veli palatini, (B) musculus uvulae, (C) tensor veli palatini, (E) palatopharyngeus, (F) palatoglossus.



Tensor veli palatini. The tensor veli palatini is a bilateral, double-bellied muscle originating at the scaphoid fossa at the base of the medial pterygoid plate of the sphenoid bone and the lateral margins of the Eustachian tube cartilage (Abe et al., 2004; Barsoumian, Kuehn, Moon, & Canady, 1998). The majority of the muscle is located between the medial and lateral pterygoid plates within the pterygoid fossa. It courses medially and inferiorly, parallel to the levator veli palatini muscle, where it terminates in a tensor tendon that wraps around the hamulus of the medial pterygoid plate (Barsoumian et al., 1998). The tendon proceeds medially, entering the region between the hard palate and anterior soft palate to attach and form a portion of the palatine aponeurosis. The tensor veli palatini is shown in Figure 4 (labeled “C”).

The primary function of the tensor veli palatini is to open the Eustachian tube during swallowing and yawning, allowing for drainage of fluid from the middle ear and equalization of air pressure across the ear drum (Leider, Hamlet, & Schwan, 1993). Due to the angle of the tensor veli palatini muscle relative to the hamulus and direction of the aponeurosis fibers, it is unlikely that the tensor muscle itself can produce tensile properties to the velum (Barsoumain et al., 1998). However, Barsoumain et al. (1998) described a dual nature to the tensor veli palatini muscle in which a segment called the dilator tubae may function to produce tension to the anterior portion of the velum.

Superior pharyngeal constrictor. The superior pharyngeal constrictor muscle is a thin, fan-shaped, bi-pinnate muscle that forms the upper lateral and posterior pharyngeal walls. A bi-pinnate muscle has an architecture that resembles a feather with a central plume from which muscle fibers diverge away. In the case of the superior pharyngeal constrictor, the central plume is called the pharyngeal raphe and can be located along the posterior pharyngeal tube with the fibers diverging away from the tendon and wrapping around the pharynx to insert anteriorly onto many attachments. It is one of three pharyngeal constrictor muscles (superior, middle, and inferior pharyngeal constrictors) that surround the length of the pharynx. Distinct muscle bundles, referred to as the pterygopharyngeus, buccopharyngeus, mylopharyngeus, and glossopharyngeus muscles, are formed by the multiple origin sites of the superior pharyngeal constrictor. The superior pharyngeal constrictor forms the posterior and lateral pharyngeal walls.

The posterior pharyngeal wall is visible during oral inspection and, in lay terms, is referred to as the back of the throat.

Portions of the superior pharyngeal constrictor muscle attach directly to the velum, which may assist in velopharyngeal retraction or formation of a Passavant's ridge (Kuehn, 1979). Circular or sagittal closure patterns are heavily influenced by contraction of the superior pharyngeal constrictor muscle.

Palatopharyngeus. The palatopharyngeus muscle contains both vertical and transverse muscle bundles. The vertically-oriented fibers are contained within the posterior faucial pillars, originating on the lateral margins of the velum and inserting into the lateral pharyngeal walls and greater horns of the thyroid cartilage of the larynx. The transverse fibers course posteriorly from the velum and insert into the lateral pharyngeal walls (Cassell, Moon, & Elkadi, 1990). The palatopharyngeus is shown in Figure 4 (labeled "D").

Similar to the superior pharyngeal constrictor, the upper transverse fibers of the palatopharyngeus muscle likely contribute to the medial movement of the lateral pharyngeal walls and possibly the formation of a Passavant's ridge. The vertical fibers work in synergy with the levator veli palatini and palatoglossus muscles to position the velum (Fritzell, 1969; Kuehn, Folkins, & Linville, 1988; Moon, Smith, Folkins, Lemke, & Gartlan, 1994; Seaver & Kuehn, 1980). Due to the directions of the vertical fibers, the fibers may also serve as an antagonist to the levator veli palatini muscle. Most research suggests that the palatopharyngeus is more active during swallowing than speech. The bilateral palatopharyngeus muscle bundles are also released and secured at the posterior pharyngeal wall during a sphincter pharyngoplasty, a common surgical correction for treating hypernasal speech and/or obligatory nasal air emission due to velopharyngeal dysfunction after primary palate repair.

Palatoglossus. The palatoglossus is a paired muscle situated within the anterior faucial pillars. It originates from the lateral margins of the velum, courses through the anterior faucial pillars, and inserts onto the lateral aspects of the body of the tongue. The palatoglossus is shown in Figure 4 (labeled "E"). The palatoglossus is a direct antagonist to the levator veli palatini muscle, meaning contraction of this muscle produces the opposite response to the velum compared to that of the levator veli palatini muscle. Specifically, contraction of the palatoglossus can act to lower the velum, elevate the tongue, and/or constrict the faucial isthmus. Although all of these functions are important in swallowing, palatoglossus activity during speech production is variable across individuals, and although generally active during all speech, it is most active during the production of nasal consonants (Kuehn & Azzam, 1978; Moon et al., 1994). Anatomically, the positioning of the anterior faucial pillars (and therefore, the palatoglossus muscle) may be more anterior or posterior, giving way to either tongue elevation or velar lowering, respectively (Kuehn & Azzam, 1978). Furthermore, the large amount of elastic tissue existing along the oral aspect of the anterior faucial pillars may assist in lowering of the velum and keeping the velopharyngeal port open during sleep (Kuehn & Azzam, 1978).

Salpingopharyngeus. The salpingopharyngeus muscle originates at the torus tubarius near the orifice of the eustachian tube (Huang, Lee, & Rajendran, 1997). Inferiorly coursing muscle fibers travel within the salpingopharyngeal fold prior to inserting into the lateral pharyngeal walls. This muscle is small and occasionally absent in some individuals (Dickson & Dickson, 1972).

Contraction of the salpingopharyngeus muscle may act to pull the lateral pharyngeal walls superiorly. This action may assist in swallowing, but the functional significance of this muscle for speech has not been established. However, it is covered in this section because the muscle is contained within the nasopharynx and often classified as a velopharyngeal muscle due to its position within the portal.

Innervation of the velopharynx

Motor. Sensorimotor innervation of the velopharyngeal musculature is generally described as a function of the pharyngeal plexus, which is a system of branches of the glossopharyngeal (CN IX), vagus (CN X), and accessory (CN XI) cranial nerves. The tensor veli palatini muscle is an exception, as it is innervated by the motor root of the mandibular branch of the trigeminal nerve (CN V) (Kennedy & Kuehn, 1989). However, there is some disagreement in the literature regarding the innervation of different muscles in this region. For instance, Shimokawa, Yi, and Tanaka (2005) observed through cadaveric study that the levator veli palatini, palatopharyngeus, and musculus uvulae also receive innervation though the lesser palatine nerve (CN VII) in addition to the pharyngeal plexus. Consequently, the innervation of certain velopharyngeal muscles is equivocal and requires additional study (Nishio, Matsuya, Machida, & Miyazaki, 1976).

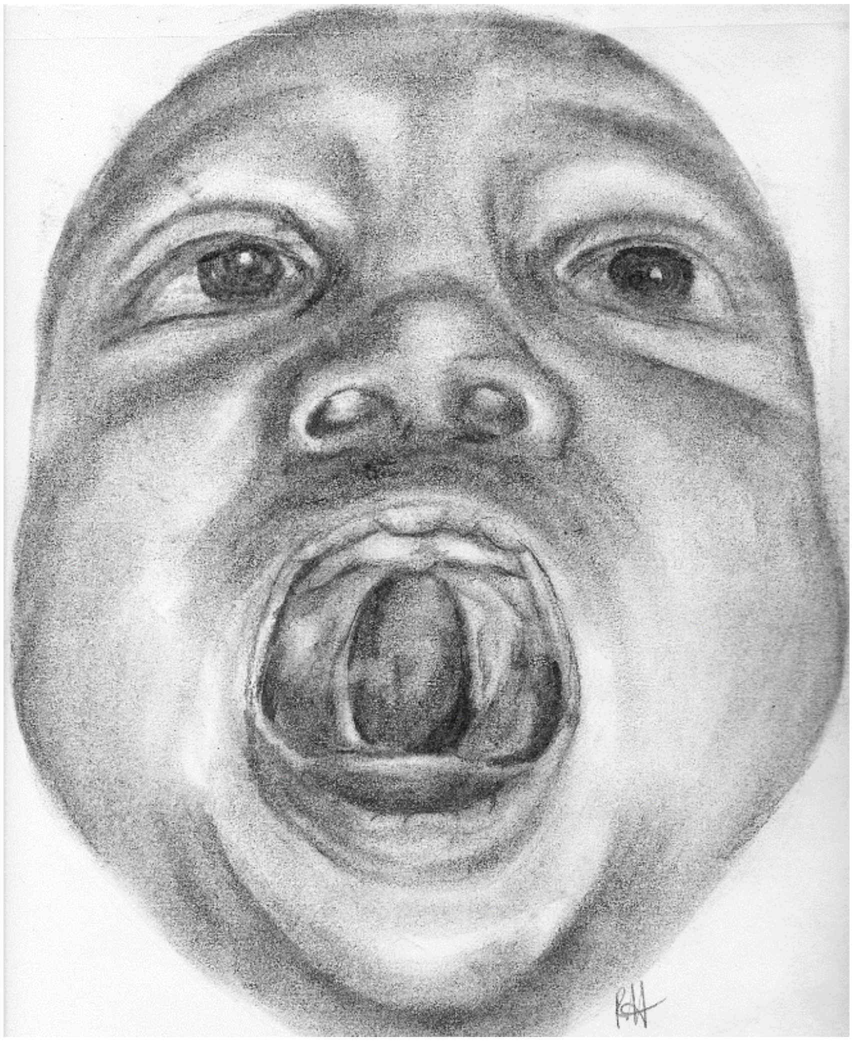
Sensory. Sensory information from the palatal and pharyngeal mucosa is conveyed by branches of the trigeminal (CN V), facial (CN VII), glossopharyngeal (CN IX), and vagus (CN X) cranial nerves. Sensory innervation of the velum and pharynx is provided by the pharyngeal branch of the vagus nerve (CN X) (Kennedy & Kuehn, 1989). The density of cutaneous receptors in the velum decreases in an anterior to posterior orientation (Grossman & Hattis, 1969; Kanagasuntheram, Wong, & Chan, 1969). Muscle spindles, sensory receptors that detect changes in muscle length, are present in the levator veli palatini, tensor veli palatini, and palatoglossus muscles but not in the other velopharyngeal muscles (Kuehn, Templeton, & Maynard, 1990; Liss, 1990).

Velopharyngeal dysfunction. Velopharyngeal dysfunction is the condition resulting in the inability to consistently and fully close the velopharyngeal value during oral sounds (D'Antonio et al., 1988; Jones, 1991) Velopharyngeal dysfunction can result in resonance and speech sound disorders such as hypernasality and/or nasal air emission. There are both anatomical and physiological causes of closure deficits, but the most frequent is seen in patients who are born with cleft palate, which is indicative of an anatomical deficit. Common anatomic causes include a short velum, deep nasopharynx, or abnormally positioned levator veli palatini muscle bundles (e.g., attachment onto or just behind the posterior hard palate). Children with repaired cleft palate may exhibit a short velum, whereas children with syndromic conditions (such as 22Q11.2 Deletion Syndrome) may exhibit a deep nasopharynx. Such anatomic differences can result in abnormal velopharyngeal function during speech, causing perceived hypernasal speech and/or obligatory nasal air emission. Although the exact cause of physiologic malfunction is not always clear, musculoskeletal disorders, brainstem tumors, and syndromic diagnoses have been associated with lack of movement or asymmetrical movement of the velum.

Cleft palate. Cleft palate is the most common anatomical cause of velopharyngeal dysfunction (Woo, 2012). Figure 5 depicts an infant with an unrepaired cleft palate. Due to the cleft palate, the velopharyngeal muscles that would normally attach at midline are forced to relocate more laterally. Specifically, the levator veli palatini muscle attaches to the lateral and posterior aspect of the bony hard palate rather than meeting at velar midline with interdigitating muscle fibers (Peterson-Falzone, Hardin-Jones, & Karnell, 2001). Although not confirmed *in vivo*, the musculus uvulae is likely absent or decreased in size and located laterally within the hemivelar segments. The tensor veli palatini muscle also attaches to the lateral aspects of the hard palate, similarly to the palatoglossus and palatopharyngeus muscles (Perry, 2011).

Salpingopharyngeus and superior pharyngeal constrictor muscles are typically unaffected by the cleft palate due to their location.

Figure 5. Infant shown intraorally with an unrepaired cleft palate.



Despite surgical palate repair, there are notable differences in the anatomy between individuals with repaired cleft palate and their non-cleft counterparts. At a muscular level, the levator veli palatini and tensor veli palatini morphology are significantly different across adults with repaired cleft palate and non-cleft adults (Kotlarek, Perry, & Fang, 2017; George, Kotlarek, Kuehn, Sutton, & Perry, submitted for publication). Although it is now common practice to reposition the levator veli palatini muscle sling during primary palatoplasty (such as in an intravelar veloplasty or Furlow double opposing Z-plasty, to name a few), primary palate repair surgery generally does not aim to reposition the tensor veli palatine muscle, which likely contributes to poor auditory tube function and decreased ventilation of the middle ear (Abe et al., 2004). In addition to abnormal muscle location and function, other obstacles are present secondary to the cleft of the palate, which lead to issues surrounding feeding, maxillary growth, dentition, hearing, speech, and psychosocial health.

Conclusion. The velopharyngeal mechanism provides highly-synchronized control over the opening and closing of the velopharyngeal port during speech and swallowing. This area remains patent at rest to allow for relaxed, nasal breathing. Velopharyngeal closure is required during oral speech production and swallowing. However, it is important to remember and consider the "in-between time" and coarticulation effects of connected speech, as to not oversimplify the velopharyngeal system into the binary categories of "open" or "close." The action of the velopharyngeal mechanism is not instantaneous, so timing factors are critical to consider as the velopharynx anticipates opening for a nasal sound or closing for an oral sound (Moll & Daniloff, 1971). The velopharyngeal orifice is a three-dimensional space that behaves differently for each individual, depending on unique anatomy and physiology, language, dialect, grammatical patterns, and habits (Perry & Kuehn, 2016). Understanding the components of the normal velopharyngeal mechanism and their corresponding functions is imperative to providing adequate clinical diagnoses and treatment within the field of speech-language pathology.

Surgical Treatment of Cleft Palate and Velopharyngeal Dysfunction

Primary palatoplasty. Children born with a cleft palate typically undergo primary reconstruction of the palate (primary palatoplasty) between 6-12 months of age. The goal of the primary palatoplasty is to achieve complete closure of the cleft in the hard and soft palate, minimize maxillary growth disturbances and dento-alveolar deformities, and create a physiological mechanism conducive to the development and production of normal speech (Agrawal, 2009). In the past 40-50 years, there has been a movement for surgical repair of the palate to restore both form and function of the palate, specifically returning "normal to normal" (Millard, 1976). Currently, there are various surgical techniques used during primary palatoplasty, which differ between centers and among surgeons (Agrawal, 2009). Current literature suggests that positive outcomes are only apparent approximately 70-80% of the time regardless of the type of procedure used (Marsh, Grames, & Holtman, 1989; Moore, Lawrence, Ptak, & Trier, 1988; Musgrave & Bremner, 1960; Phua & de Chalain, 2008; Sullivan, Marrinan, LaBrie, Rogers, & Mulliken, 2009). Currently, two popular techniques for soft palate closure during primary palatoplasty include the intravelar veloplasty and the Furlow double-opposing Z-plasty. One commonality between these techniques includes restoring the levator muscle "sling" to its intended anatomical position in the posterior soft palate; however, the approach by which posterior positioning of the levator muscle is established differs between these two techniques. Details regarding only the intravelar veloplasty and Furlow double-opposing Z-plasty are provided, as these are the surgical approaches utilized in study III.

Intravelar veloplasty. The intravelar veloplasty is a technique for primary palatoplasty that was first proposed by Otto Kriens in 1967. Based on cadaveric studies, Kriens discovered that the anterior portions of the levator and palatopharyngeus muscles were attached to the hard palate in individuals with cleft palate and first proposed reorienting these muscles to a more normalized, transverse positioning by suturing the right and left muscle bundles end-to-end (Kriens, 1971). This procedure was later revised by Peter Randall, who aimed to tighten the levator sling and improve velopharyngeal competence by overlapping the levator muscle bundles (Randall, 1979).

Furlow double-opposing Z-plasty. Leonard Furlow was the first to apply the Z-plasty to surgical closure of the palate. A Z-plasty is a surgical technique that can improve the appearance of scars and lengthen the tissue area by creating one Z-shaped incisions rather than a straight-line incision. In Furlow's technique, one Z-plasty is placed in the oral mucosa and second Z-plasty is placed in the opposite direction within the nasal mucosa. Each levator muscle bundle is contained within the mucosal flap from the corresponding side and freed from the posterior hard palate, so that when the flaps are rotated and sutured back together, the levator muscle bundles overlap in the posterior soft palate (Furlow, 1986). By theory, less scarring occurs on the palate due to less blunt dissection of the levator muscle bundles and the absence of a straight, midline scar alone the palatal midline.

Variables Related to Velopharyngeal Dysfunction

Various studies have sought to examine which, if any, anatomic and physiologic features predict VPD. These have been divided into categories of anatomical variables, physiological variables, and surgical variables.

Anatomical. Collectively, velar length and pharyngeal depth form the velar depth:length ratio, which is equal to 0.68 in the normative population (Subtelny, 1957). Reduced palate length and increased pharyngeal depth have been observed with VPD in individuals with repaired cleft palate (D'Antonio et al., 2000; Randall et al., 2000). The depth:length ratio is greater in individuals with repaired cleft palate, producing a velopharyngeal gap causing hypernasal speech (D'Antonio et al., 2000; Satoh et al., 2005). In an investigation comparing cleft and non-cleft participants, Ha et al. (2007) found that participants with cleft palate had increased levator origin-origin distance and angle of insertion as well as decreased levator muscle bundle thickness and length. One individual did not have a cohesive levator muscle sling, which was thought to contribute to signs of VPD in this participant with cleft palate (Ha et al., 2007). Leclerc et al. (2014) aimed to predict post-palatoplasty VPD in a retrospective chart review of 67 patients with repaired cleft palate. The hard palate width and nasopharyngeal depth were very prominent in the top performing predictors (Leclerc et al., 2014)

Some studies have contradicted these findings. Ezzat, El-Begermy, Eid, and Akel (2016) found that velar lengthening procedures do not significantly improve likelihood for VPD post-palatoplasty. When comparing intravelar veloplasty with and without V-Y pushback palatoplasty, there was a significant difference between surgical groups with regard to palatal lengthening, but no statistically significant difference was present between groups with respect to post-operative mean pharyngeal gap, resonance, or nasal air emission (Ezzat et al., 2016). Tian et al. (2010a) found that, of participants with repaired cleft palate, the group with VPD showed slightly less retropositioning of the levator muscle bundles, a thinner levator muscle sling, and a wider pharynx than the group that achieved velopharyngeal closure. It was thought that these dimensions may increase the difficulty of achieving adequate velopharyngeal closure for some individuals with cleft palate but were not significantly different between cleft groups with and without VPD (Tian et al., 2010a). Kotlarek et al. (2017) found significant differences in total levator muscle volume as well as circumference and diameter at midline between individuals with and without cleft palate, but none of these levator muscle dimensions were linked to the presence of VPD in adults post-palatoplasty in the one participant with signs of VPD. Overall, much variability exists within the area of anatomical variables relative to VPD.

Physiological. Velar stretch, or the ability of the velum to increase in intrinsic length from rest to elevation, has been linked to adequate velopharyngeal closure (Pruzansky & Mason, 1969). It has been proposed that limited velar stretch in individuals with cleft palate is most likely due to resistance and rigidity caused by velar scar tissue (Tian et al., 2010b). When comparing participants with repaired cleft palate with and without VPD to participants with non-cleft anatomy, Tian et al. (2010b) found the group with VPD varied significantly in velar and pharyngeal mobility from those with cleft palate without VPD. Specifically, the group with VPD showed the least maximal velar stretch, lowest maximal velar height, smallest maximal pharyngeal constriction, and lowest maximal velopharyngeal ratio among the three groups (Tian et al., 2010b). Velar stretch appears to be related to velopharyngeal function for speech.

Through research in computational modeling, variables related to the presence of VPD have been proposed. When measurements were taken from individual patients with cleft palate using a line-segment model, a strong relationship was found between the effort required by muscles to form closure (as predicted by the model) with the quality of speech: the more effort required for muscles to form closure, the more hypernasality (Pelland, Blemker, & Perry, 2017). The velar depth:length ratio as well as the muscle cross-sectional area had the largest influences on required muscle effort (Pelland et al., 2017).

Surgical. Differences in surgeon skills and surgical type of primary palate repair have shown to have varying rates of velopharyngeal dysfunction. Certain surgical techniques, such as the Furlow double-opposing Z-plasty, have been of recent popularity due to their ability to retroposition the levator muscle sling and lengthen the velum. In a retrospective review of 559 nonsyndromic patients undergoing primary modified Furlow palatoplasty at one center, 72.4 percent had a competent velopharyngeal mechanism (Jackson et al., 2013). Da Silva, Dutka, Amaral, Perico, and Pegoraro-Krook (2017) compared videofluoroscopic evaluations of 90 participants who underwent primary palatoplasty with either the Furlow double-opposing Z-plasty or the Langenbeck procedure. The patients who underwent surgery with the Furlow technique presented with significantly longer velums than patients who underwent surgery with the Langenbeck procedure, but there was no significant difference in velar thickness or depth of the nasopharynx between the two procedures (da Silva et al., 2017). It was estimated that information regarding velopharyngeal morphology was predictive of VPD for 80% of the participants in this study (da Silva et al., 2017). However, as previously mentioned, Ezzat et al. (2016) compared intravelar veloplasty with and without V-Y pushback palatoplasty to find significant difference in palatal lengthening but not with respect to post-operative mean pharyngeal gap, resonance, or nasal air emission. Surgeon experience may play a factor in why different groups have reported varying results regarding surgical technique (Khosla, Mabry, & Castiglione, 2008; Marrinan, LaBrie, & Mulliken, 1998). A lack of universal outcome measures is also a likely culprit for the variety seen in speech results.

Secondary Surgical Intervention

Despite adequate timing of the primary palatoplasty, some individuals with cleft palate require secondary management to address residual VPD. In individuals that have previously undergone palatal repair surgery, VPD is most commonly corrected with surgical management (Woo, 2012). It is estimated that 25-37% of children with a repaired cleft palate need a second surgery to eliminate the presence of hypernasal speech (Bicknell et al., 2002; Lithovius et al., 2014). It is important to identify and address VPD in a timely manner, as aberrant speech with compensatory misarticulations is more likely to develop in individuals with VPD (Riski, 1979).

Currently, the two most common surgical approaches to the management of VPD include the sphincter pharyngoplasty and pharyngeal flap (Cable, Canady, Karnell, Karnell, & Malick, 2004; Sloan, 2000). The goal in both of these pharyngoplasty techniques is to create a permanent narrowing of the velopharyngeal orifice to allow for adequate velopharyngeal closure during speech. In the pharyngeal flap procedure, superiorly-based mucosal flap from the posterior pharyngeal wall is dissected and sewn into the posterior soft palate, creating a permanent midline tissue mass with two lateral ports for airflow. This procedure is typically performed in individuals with good lateral pharyngeal wall movement or a large velopharyngeal gap. In the sphincter pharyngoplasty, superiorly-based tonsillar pillar flaps containing the palatopharyngeus muscle are raised superiorly and sewn together to the posterior pharyngeal wall, creating a narrowed, single velopharyngeal portal. There are a variety of risks associated with the use of a pharyngoplasty to address VPD, including obstructive sleep apnea and persisting VPD.

Pedicled Buccal Fat Pad Graft

The BFP is a bilateral, encapsulated mass located between the buccinator and masseter muscles of the cheek. The pedicled BFP graft (or flap) has been a well-documented technique for closure of oral defects, including literature pertaining specifically to the repair of cleft palate fistulae (Ashtani et al., 2011; Egyedi, 1977; Grobe et al., 2011; Habib & Medra, 2016; Hanazawa et al., 1995; Jain et al., 2012). Literature has presented the utilization of the BFP in primary palatoplasty (Kim, 2001; Levi et al., 2009; Pappachan & Vasant, 2008; Pinto & Debnath, 2007; Yamaguchi et al., 2016; Zhang, et al. 2010).

Levi and colleagues (2009) hypothesized the use of a BFP graft during primary palatoplasty results in increased vascularized tissue within an otherwise denuded space at the posterior hard palate. In such, it was expected that this increase in volume and vascularity would prevent wound contracture, thus maintaining a longer velar position and optimizing maxillary growth. In other areas of the body, scar tissue is thought to restrict movement and is less pliable overall. Scar tissue present in individuals with cleft palate from surgical closure of the palate creates a stiffening effect (Birch & Srodon, 2009). Tian et al. (2010b) found that velar stretch was significantly different between cleft and non-cleft participants and hypothesized that limited velar stretch in individuals with cleft palate is most likely due to resistance and rigidity of velar scar tissue. Inouye et al. (2015) suggested that if the velum is stiffer in individuals with repaired cleft palate due to the presence of scar tissue, velopharyngeal distance, velum-levator angle, and velar length may be more influential for closure force than if the velum is more compliant. Given the absence or hypoplastic nature of the musculus uvulae, it is hypothesized that the velum in an individual with cleft palate lacks the stiffness velar properties, as described by Azzam and Kuehn (1977). Furthermore, a stiffer velum would require more specific tension to stretch the velum for elevation (Inouye et al., 2015). If the use of a BFP graft during primary palatoplasty does, in fact, reduce velar scarring and wound contracture, it would provide more favorable tissue properties for velopharyngeal closure.

Pappachan and Vasant (2008) also claimed BFP graft during primary palatoplasty results in an increase in velar lengthening, although they did not assess this hypothesis. Additionally, it has been suggested that the use of a pedicled BFP graft during primary palatoplasty may improve maxillary growth while maintaining a favorable depth:length ratio for velopharyngeal closure (Zhang et al., 2015). Increased palate length has been suggested to be indicative of successful speech outcomes, emphasizing the importance of adequate palatal length on normal velopharyngeal function for speech (D'Antonio et al., 2000; Randall et al., 2000). Other studies have indicated that velar length is not correlated with decreased rate of VPD after primary palatoplasty (Ezzat et al., 2016; Tian et al., 2010a). Da Silva et al. (2017) found that velopharyngeal morphology was predictive of VPD for 80% of the participants in their study. If use of the BFP graft were found to effectively increase velar length, it may provide a decreased rate of VPD post-palatoplasty compared to traditional surgical methods.

These hypotheses regarding velar lengthening, decrease in velar scar composition, and thus improved velar function have not been systematically examined and compared to children with cleft palate not receiving a pedicled BFP graft nor children without cleft palate. Additionally, reports of BFP use during primary palatoplasty have been limited to small case studies with no quantitative measurements to support claims of increased velar length and decreased scar tissue compared to individuals who underwent an alternative primary palatoplasty technique. Therefore, study III aims to specifically investigate velar length and tissue composition within those that receive a BFP graft at the time of primary palatoplasty.

Rationale for MRI Investigations

According to Beer et al. (2004), the ideal method for imaging the velopharyngeal portal should be noninvasive, easily repeatable, reproducible, allowable of various image planes, and free from ionizing radiation. Videofluoroscopy and nasendoscopy are commonly used in evaluating the velopharynx in individuals with cleft palate and/or VPD. MRI possesses many benefits over these traditional visualization methods. Potential benefits of MRI over videofluoroscopy include no exposure to radiation, clearer images, and no overlap of shadows from other anatomy. Unlike nasendoscopy, MRI is noninvasive, and measurement of velopharyngeal changes can be made at rest and during phonation from all axes. Overall, MRI has better visualization of muscles and tissue compared to all other methods. Potential drawbacks of MRI include cost, acquisition time, and claustrophobia. Claustrophobia is estimated to affect 1 out of 100 people undergoing MRI and the pooled proportion for scan terminations due to claustrophobia equals only 1.18% (Munn et al., 2015). However, because there is no radiation or known harm present, MRI can be repeated several times to get an adequate image. A very minimal failure rate has been reported by several studies with child-friendly imaging protocols and prior preparation of participants. With respect to speed, faster imaging techniques (e.g., BLADE) and improvements in MRI technology have decreased scanning time. Scanning time for a three-dimensional volumetric scan can be completed in less than five minutes, and even down to as little as 1 minute, 30 seconds when the BLADE technique is utilized.

Completion of one imaging protocol provides surgeons and speech-language pathologists with a plethora of information regarding the patient at a particular time point. Resecting of images across any plane allows for this information to be obtained, even past the time of the MRI scan itself. Completion of the MRI imaging protocol at specified time points can track anatomical changes over time and help to predict need for secondary surgical interventions. Overall, the goal would be to improve quality of life for the patient by intervening with surgery in a timely manner and reducing the overall amount of surgeries required for speech.

Use of MRI in Velopharyngeal Investigations

MRI is the only imaging modality that allows visualization of the internal musculature in vivo. Computerized Tomography is an excellent imaging method for bone; however, it cannot be used to visualize musculature to the same degree in which MRI can. Kuehn, Ettema, Goldwasser, and Barkmeier (2004) demonstrated the clinical utility of comparisons between pre- and postsurgical MRI scans. Studies have previously examined the velopharyngeal musculature in adults with normal anatomy (Bae et al., 2011b; Ettema et al., 2002; Perry, 2011; Perry et al., 2013a; Tian & Redett, 2009), adults with cleft palate anatomy (Ha et al., 2007; Kotlarek et al., 2017), children with normal and cleft palate anatomy (Kollara & Perry, 2014; Mason & Perry, 2016; Mason, Perry, Riski, & Fang, 2016; Tian et al., 2010a,b,c), and infants with cleft and non-cleft anatomy (Kuehn et al., 2004; Perry et al., 2011; Schenck et al., 2016). These MRI studies demonstrate the value of using MRI and its potential clinical utility to improve postsurgical speech outcomes. Knowledge of these outcomes provide important insight into anatomical variations that may produce more favorable dimensions for adequate velopharyngeal closure.

Computational Modeling of Velopharyngeal Closure

Many studies attempting to understand the relationship between velopharyngeal anatomy and VPD have been observational. Due to the limitations in the types of measurements that can be performed *in vivo* and the time it would take to acquire an adequate sample size isolate the effects of certain parameters, it is virtually impossible to reveal cause-and-effect relationships from observations alone. Therefore, computational models allow us to directly and systematically study cause-and-effect relationships by integrating the wealth of literature describing the anatomy, physical properties, and *in vivo* function of the velopharyngeal mechanism.

Finite element models have previously been used to investigate the velopharyngeal mechanism in non-cleft individuals. Inouye, Perry, Lin, and Blemker (2015) created a biomechanical finite element model to simulate the levator function using input from descriptions of the levator muscle, the passive soft tissue of the palate including the uvula, and the posterior pharyngeal wall. The model included mathematical representations of both passive and active muscle properties of these structures: the active component incorporates the known force-length behavior of skeletal muscle (where the peak muscle force occurs when the muscle reaches its optimal length). The levator activation (ranging from 0-100%) was input to the model, and the output quantities of interest were the magnitude of the total force exerted by the velum on the posterior pharyngeal wall (velopharyngeal closure force) and the deformations of the velum. The predictions of velopharyngeal closure obtained from model compared favorably with measurements published by Kuehn and Moon (1998).

Further research in computational modeling has added variables into the finite element model proposed above to determine which variables have the most impact on velopharyngeal closure force. Inouye et al. (2016) indicated that the musculus uvulae's function as a velar extensor may be crucial in providing adequate length for velopharyngeal closure (Inouye et al., 2016). The musculus uvulae is a midline velar muscle thought to be responsible for adding bulk to the velum and creating a tight seal between the velum and posterior pharyngeal wall during velopharyngeal closure (Azzam & Kuehn, 1977). In individuals with cleft palate, the musculus uvulae has been described as reduced or absent (Huang et al., 1997; Pigott et al., 1969). The musculus uvulae nearly triples the midline velopharyngeal contact length as a space-occupying structure (Inouye et al., 2016). It has been proposed that in the case of its absence, autologous fat or muscle could be used in place of the musculus uvulae to eliminate the velar midline defect (Inouye et al., 2016).

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CHAPTER 3

STUDY I

Morphology of the Levator Veli Palatini Muscle in Adults with Repaired Cleft Palate[2]

Abstract

The purpose of this study was to examine differences in levator veli palatini (levator) morphology between adults with repaired cleft palate and adults with non-cleft anatomy. Fifteen adult participants (10 with non-cleft anatomy, 5 with repaired cleft palate) completed a 3D static MRI. Image analyses included measures of total muscle volume and the circumference and diameter at 6 points along the length of the muscle. Differences between groups were analyzed using independent sample Mann-Whitney U-Tests ($\alpha < 0.05$). Significant differences between groups were noted for measures of muscle volume, circumference at the origin and insertion, anterior-posterior diameter at the origin and midline, and superior-inferior diameter at the point of insertion into the velum and midline. Differences in measures at other points along the levator muscle belly were not statistically significant. Limited sample size and gender differences may have impacted statistical findings. Overall, the levator muscle in adults with repaired cleft palate is significantly different than that of adults with non-cleft anatomy. This study demonstrates the successful implementation of a method for 3D analysis of velopharyngeal (VP) musculature with potential clinical utility given continued technological advancements in MRI. Continued evaluation of pre- and post-surgical anatomy and short- and long-term outcomes may contribute to a better understanding of the effects of various types of palatoplasties on levator structure, which is important to VP function for speech.

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[2] Kotlarek, K.J., Perry, J.L., & Fang, X. (2017). Morphology of the levator veli palatini muscle in adults with repaired cleft palate. *Journal of Craniofacial Surgery*, 28(3), 833-837.

Introduction

The levator veli palatini (levator) muscle is widely accepted to be the predominant muscle for velar elevation.[1-2] In individuals with typical anatomy, the levator muscle originates from the skull base near the apex of the petrous portion of the temporal bone.[3] The levator muscle courses across the middle one-third of the velum with interdigitating muscle fibers at the velar midline and no septum separating the two muscle bundles.[4] Past studies have demonstrated a relatively consistent size, shape, and location of the levator muscle in individuals with non-cleft anatomy.[4-6]

Differences in musculature within the velopharyngeal (VP) mechanism have been studied between individuals with cleft palate and those with non-cleft anatomy. Ha et al[7] observed variable levator muscle length and thickness among a group of four adult males with repaired cleft palate. Measures of distance between points of levator origin, levator muscle length, and levator muscle thickness were smaller than those observed in adults with non-cleft anatomy, as described by Ettema et al.[5] Tian et al[8] observed a thinner levator muscle in children with repaired cleft palate as compared to those with non-cleft anatomy.

Nyswonger JC, Perry JL, Kuehn DP, et al (unpublished data, 2016) found no statistically significant differences in the levator muscle between adults with cleft palate and adults with non-cleft anatomy using linear measure analysis methods. However, qualitative differences of midline separation and muscle shape irregularities were reported, such as separation and/or thinning of the levator muscle at the velar midline. Nyswonger JC, Perry JL, Kuehn DP, et al (unpublished data, 2016) proposed that a more complex methodology employing measures of circumference and diameter along the course of the muscle, as described by Perry et al,[9] and volumetric analyses may enable more sensitive examination of muscular differences between cleft and non-cleft anatomy.

The purpose of this study was to examine differences in the levator muscle volume, circumference, and diameter between adults with repaired cleft palate and adults with non-cleft anatomy. Perry et al[9] indicated that understanding levator muscle morphology could provide important information into muscle function for abnormal VP control for speech and swallowing. It was hypothesized that adult participants with repaired cleft palate would present with significant differences in levator muscle morphology.

Methods

Participants

In accordance with the local Institutional Review Boards, 15 English-speaking adults were recruited to participate in this study. Five of the participants had a history of repaired cleft palate and were consecutively enrolled. Ten participants were then selected from a normative database[6] that were within the same age range as those with repaired cleft palate. The cleft palate group included 2 males and 3 females with a mean age of 25.7 years, while the group with non-cleft anatomy contained 10 males with a mean age of 23.8 years. Of the participants with repaired cleft palate, 3 had bilateral complete cleft lip and palate (subjects 1-3), and the remaining 2 had cleft palate only (subjects 4-5). All reported primary palate repair between the ages of 8-18 months. All participants underwent a Wardill-Kilner (straight line) primary palate repair surgery by different surgeons. Reported surgical information indicated no radical dissection around the hamulus and details of the levator muscle bundle overlap were not provided in any surgical reports. All but one of the participants with repaired cleft palate were judged to have resonance within normal limits. The participant with abnormal resonance was rated as having moderate-to-severe hypernasality. None of the participants had a pharyngoplasty at the time of the magnetic resonance imaging (MRI). Comparisons between groups were performed since the VP muscles are contained within the cranium. Using methods previously described by Tian and Redett[10] and Tian et al,[8,11] cranial index measures were obtained, and no significant differences were noted between the cleft and non-cleft groups.

Magnetic Resonance Imaging

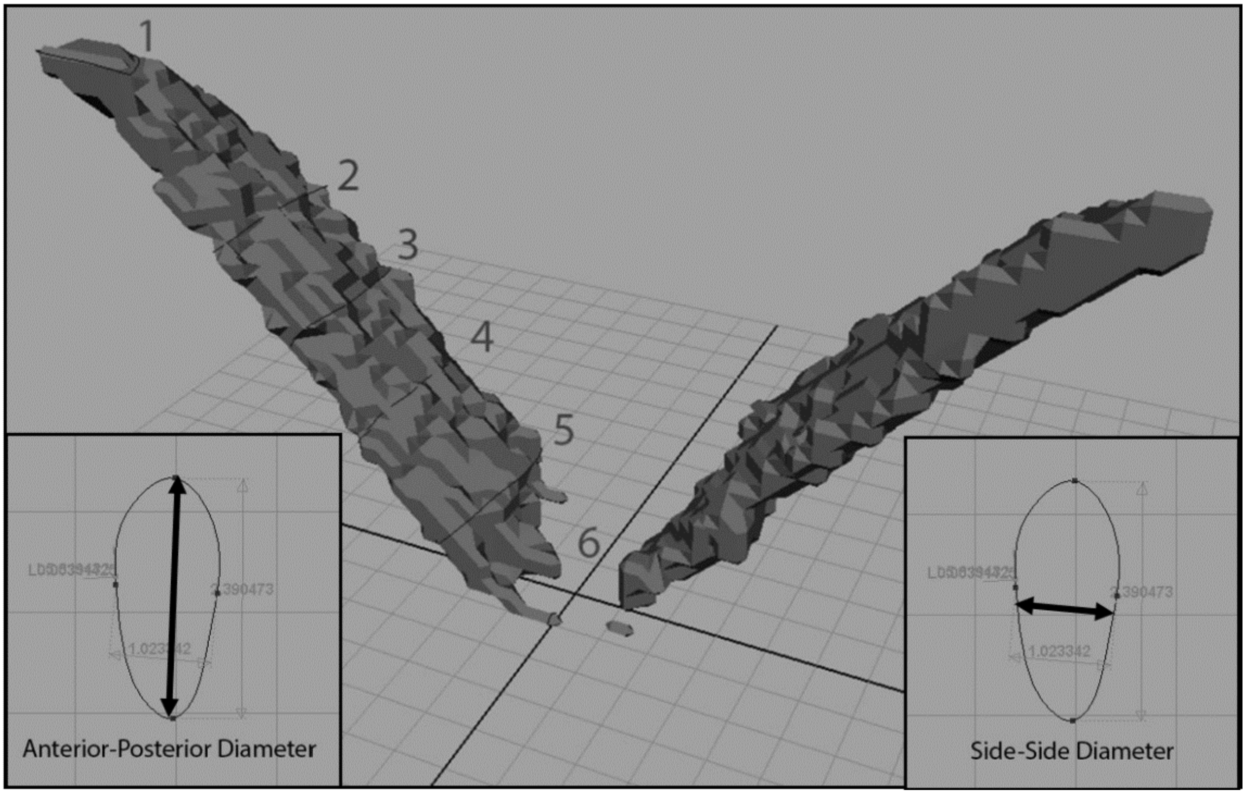
A Siemens 3 Tesla Trio (Erlangen, Germany) MRI scanner and a 12-channel Siemens Trio head coil were used to scan participants while lying in the supine position. The imaging protocol is also consistent with that used in previous MRI investigations of the VP muscles.[9] An elastic strap attached to the head coil was used to stabilize the head during the scan to reduce motion artifact that negatively influence image quality. Participants were instructed to breathe through their nose, and images were collected at rest with the velum in a fully lowered position, resting on the tongue base.

Image Analysis

Image-processing methods were consistent with previous studies[9,12-14] (also Nyswonger JC, Perry JL, Kuehn DP, et al, unpublished data, 2016). Specifically, raw magnetic resonance images were transferred into Amira 6.0.1 Visualization and Volume Modeling Software (Mercury Company Systems, Inc, Chelmsford, MA), which includes a native Digital Imaging and Communications in Medicine support program to ensure that anatomical geometry is maintained. The entire data set was resampled from the three-dimensional (3D) anatomical scan to obtain the oblique coronal image. This view allows the full sling of the levator muscle to be visualized. The levator muscle fibers were defined by segmentation of successive oblique coronal images using a paintbrush tool, and a voxel set was created to obtain volumetric analyses of the total muscle.

The voxel set was imported into Maya 8.5 (Autodesk, Ontario, Canada) for analysis of circumference and diameter through methods described by previous literature.[9] Each participant's right muscle bundle was measured, as there was little difference between levator muscle length for the right and left muscle bundles. A curve-vector arc tool was utilized to create 6 outlines perpendicular to the long axis of the muscle bundle. Due to the imperfect cylindrical shape of the levator, 8-10 vectors were placed around the model outline so they could be manually positioned against the model's surface. The 6 landmarks were selected based on successful analysis of levator circumference and diameter of non-cleft participants completed by Perry et al.[9] After measuring total muscle circumference, the outlines were then moved to a flat surface plane within the Maya software. Two diameter measures were taken to reflect the cylindrical shape for analysis of the total muscle. The anterior-posterior (A-P) diameter was generally the larger diameter. The smaller diameter has two directional names dependent on the location of the measurement due to the levator's curvilinear form, medial-lateral (M-L) in the extravelar segment (points 1-3) and superior-inferior (S-I) in the intravelar segment (points 4-6). See Figure 6 for measures of interest and diameter illustrations.

Figure 6. Image of the levator muscle displayed in Maya. The 6 points along the length of the muscle are shown as lines perpendicular to the muscle. As previously described by Perry et al,[9] the 6 points include: (1) origin of the muscle, (2) halfway between origin and velum, (3) halfway between measure 2 and 4, (4) point where levator inserts into the velum, (5) halfway between measure 4 and midline of muscle at velum, and (6) midline insertion within the velum.



Statistical Analysis

Mann-Whitney U-Tests (α < .05) for independent samples were conducted to analyze differences in total levator muscle volume, circumference, and diameter across each of the 6 points using SPSS 20.0 (IBM Corp, Armonk, NY). An un-corrected *p* value was employed for between-group comparisons. Nonparametric statistical analyses allowed for quantitative analyses of measures between the cleft and non-cleft anatomy groups at rest given outliers and a small sample size. Descriptive statistics, including the median, were also given due to presence of outliers.

Results

Total Volume of the Levator Muscle

Total levator muscle volume for participants with repaired cleft palate (Median = 1264.27 mm^3, Mean = 1247.50 mm^3, SD = 197.19 mm^3) was significantly ($U = 8$, $p = .040$) smaller than that observed for participants with non-cleft anatomy (Median = 1646.23 mm^3, Mean = 1855.90 mm^3, SD = 653.68 mm^3). The non-cleft group had more variability, as noted by the larger standard deviation, but there were no outliers.

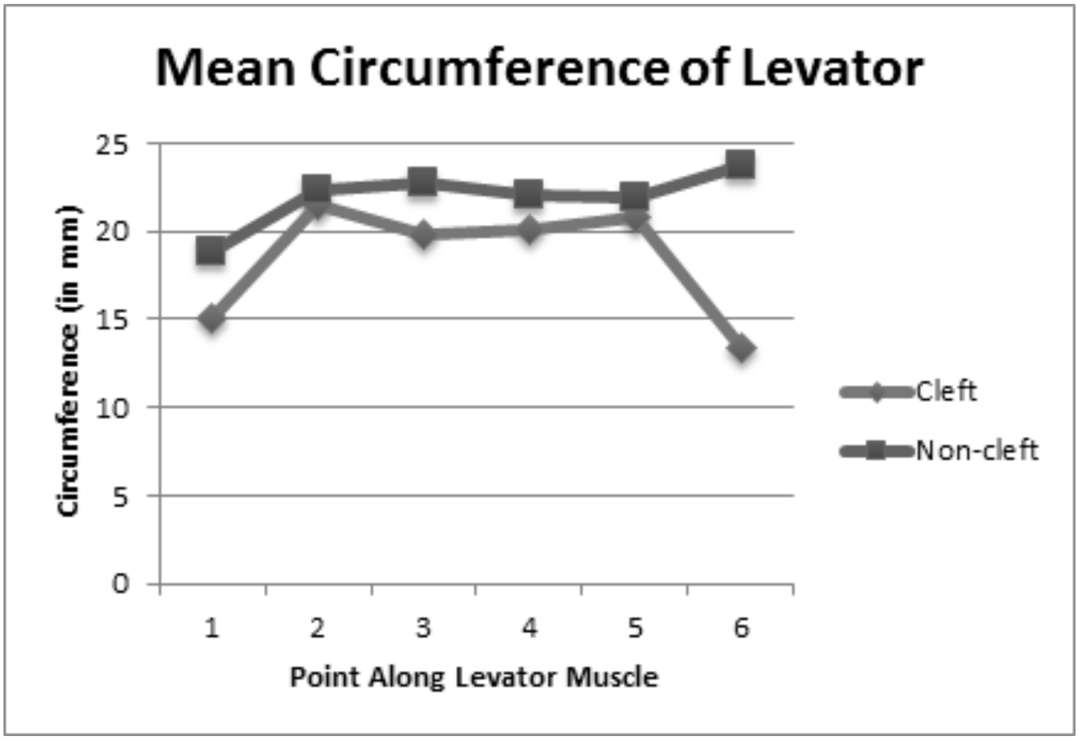
Circumference of the Levator Muscle

Table 1 shows group medians, means, and standard deviations for levator circumference for both study groups along 6 points of the muscle bundle. Figure 7 depicts the mean circumference of the levator muscle along the 6 specific data points. At point 1 (muscle origin at the base of the skull), levator circumference for participants with repaired cleft palate was significantly ($U = 4$, $p = .027$) less than that observed for non-cleft anatomy. At point 6 (the midline), levator circumference for participants with repaired cleft palate was significantly ($U = 7$, $p = .028$) less than that observed for non-cleft anatomy. All other points were not significant. The greatest difference in mean circumference for consecutive points (7.44 mm) was noted between point 5 (Mean = 20.84 mm) and point 6 (Mean = 13.40 mm), which is evidence of midline dehiscence.

Table 1. Circumference shown (in mm) at 6 points along the length of the levator muscle for cleft participants. Mean, standard deviation (in parentheses), and median shown for cleft and non-cleft groups.

Cleft						
Subject	***1***	***2***	***3***	***4***	***5***	***6***
1	10.69	22.82	15.49	17.07	19.05	12.31
2	16.19	19.46	20.49	21.16	21.73	14.85
3	15.35	20.71	19.83	19.47	20.92	2.62
4	16.67	20.57	20.07	16.49	18.70	15.35
5	16.74	24.19	23.05	26.09	23.77	21.88
Mean/SD	15.13(2.5)	21.55(1.9)	19.79(2.7)	20.06(3.9)	20.84(2.1)	13.40(7.0)
Median	16.19	20.71	20.07	19.47	20.92	14.85
Non-Cleft						
Mean/SD	18.90(2.6)	22.40(4.9)	22.76(4.0)	22.02(3.6)	21.96(5.3)	23.71(6.5)
Median	18.39	21.23	21.315	20.87	22.345	22.57

Figure 7. Mean circumference shown (in mm) at 6 points along the length of the levator muscle for cleft and non-cleft participants.



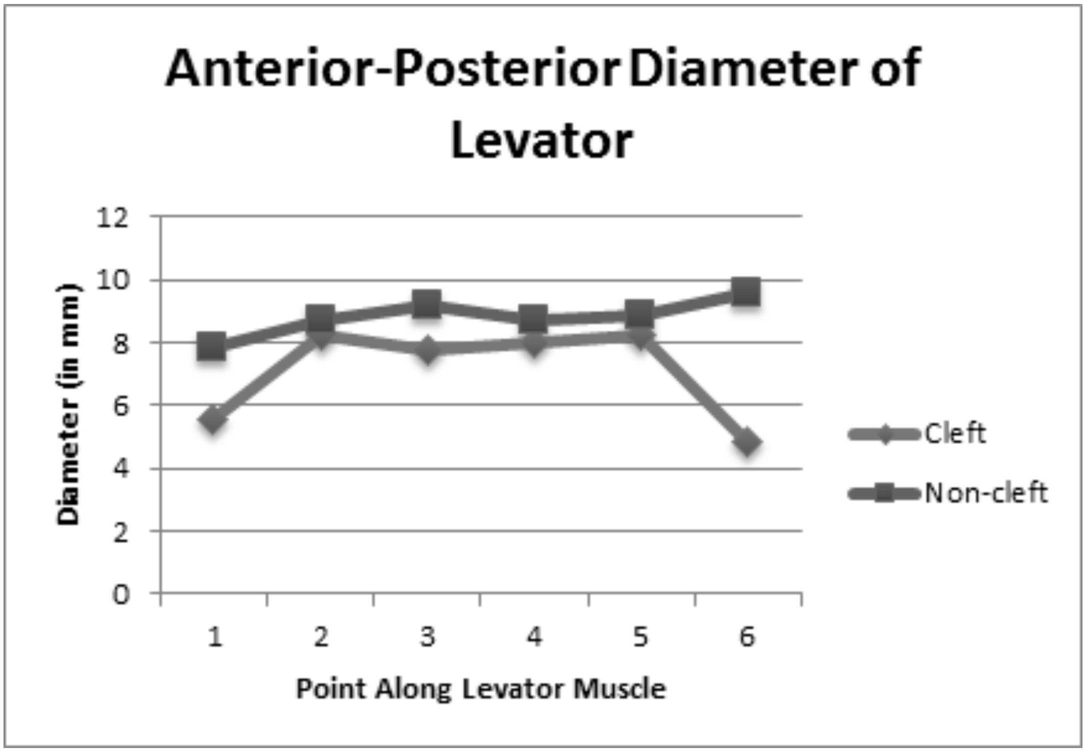
Diameter of the Levator Muscle

Difference in A-P diameter at point 1 was significant ($U = 4$, $p = .008$) between the repaired cleft palate and non-cleft groups (Table 2). At point 6 (the midline), A-P diameter for participants with repaired cleft palate was significantly ($U = 5$, $p = .013$) smaller than that observed for non-cleft anatomy. All other points were not significant. Similar to the circumference measures, the greatest difference in mean A-P diameter measures for consecutive points was noted between points 5 and 6 for the cleft group (3.3 mm). Figure 8 depicts the A-P diameter of the levator broken down into the 6 specific data points.

Table 2. The larger diameter, anterior-to-posterior (A-P), and the smaller diameter, medial-to-lateral (M-L) and superior-to-inferior (S-I), shown (in mm) at 6 points along the length of the levator muscle for cleft participants. Mean, standard deviation, and median shown for cleft and non-cleft groups.

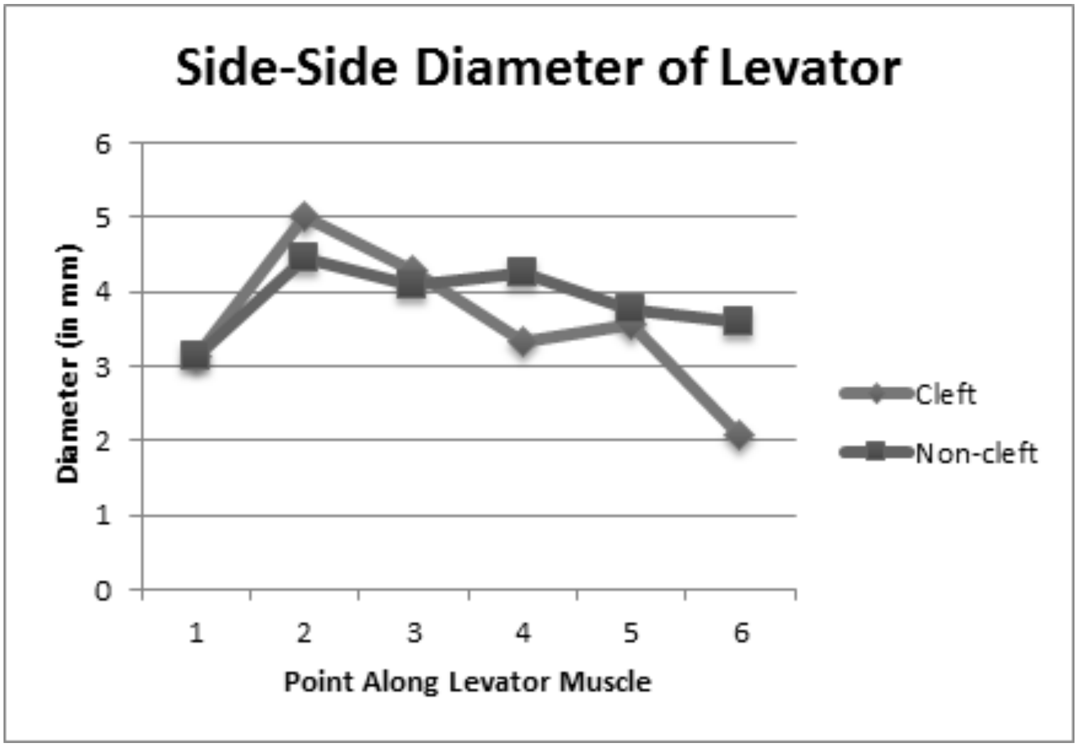
Cleft												
	1		***2***		***3***		***4***		***5***		***6***	
Subject	***A-P***	***M-L***	***A-P***	***M-L***	***A-P***	***M-L***	***A-P***	***S-I***	***A-P***	***S-I***	***A-P***	***S-I***
1	3.4	2.6	8.8	5.0	5.7	3.7	7.3	2.6	7.2	3.9	5.0	2.3
2	6.3	3.8	6.8	4.9	7.7	4.9	8.6	2.9	9.6	3.3	5.7	2.8
3	6.1	3.3	8.1	4.3	8.0	3.9	8.4	3.8	8.4	3.6	0.9	0.9
4	7.2	2.3	7.4	5.2	7.5	4.7	6.2	3.9	7.2	3.1	5.2	2.7
5	4.8	3.6	9.8	5.7	9.9	4.2	9.3	3.4	8.7	3.8	7.5	1.8
Mean/SD	5.6(1.5)	3.1(0.6)	8.2(1.2)	5.0(0.5)	7.8(1.5)	4.3(0.5)	8.0(1.2)	3.3(0.6)	8.2(1.0)	3.6(0.6)	4.9(2.4)	2.1(0.8)
Median	6.1	3.3	8.1	5.0	7.7	4.3	8.4	3.4	8.4	3.6	5.2	2.3
Non-Cleft												
Mean/SD	7.9(1.2)	3.1(0.7)	8.3(2.2)	4.4(1.2)	9.2(1.7)	4.1(1.0)	8.7(1.8)	4.2(0.8)	8.8(2.6)	3.8(1.1)	9.6(3.5)	3.6(1.1)
Median	7.6	3.15	8.9	4.4	8.9	3.8	8.8	4.15	8.8	3.6	9.3	3.5

Figure 8. Mean A-P diameter shown (in mm) at 6 points along the length of the levator muscle for cleft and non-cleft participants.



Difference in S-I diameter was significant (*U* = 8, *p* = .040) at point 4 (levator insertion into the velum) between the repaired cleft palate and non-cleft groups. Difference in S-I diameter was also significant (*U* = 5, *p* = .013) at point 6 (midline). All other points were not significant. The greatest difference in mean side-side diameter measures for consecutive points was noted between points 1 and 2 for the cleft individuals (1.9 mm). Figure 9 depicts the side-side diameter of the levator broken down into the 6 specific data points.

Figure 9. Mean M-L and S-I diameter shown (in mm) at 6 points along the length of the levator muscle for cleft and non-cleft participants.



Reliability

Pearson product correlation was used to obtain inter- and intra-rater reliability measures. A random sample of 40% of the data were considered for reliability. Intra-rater reliability was r = .80, which was calculated using separate measurements completed by 2 investigators with experience in 3D MRI data analyses using volumetric measurements. Inter-rater reliability was r = 1.00 for volumetric measures.

Discussion

Using linear analysis measures, Nyswonger JC, Perry JL, Kuehn DP, et al (unpublished data, 2016) found no statistically significant difference in the levator muscle between adults with repaired cleft palate and adults without cleft palate but described qualitative differences in the muscle form. This study aimed to use a morphologic approach to quantify these observations using 3D measures of volume, circumference, and diameter. In the present study, total volume of the levator muscle in adults with repaired cleft palate was found to be significantly reduced compared to non-cleft anatomy. These results support our hypothesis that adult participants with repaired cleft palate present with significant differences in levator muscle morphology.

Based on the present study, it was evident that the largest discrepancy between repaired cleft and non-cleft levator anatomy existed at the velar midline (point 6). Two participants in the repaired cleft group, both with bilateral cleft lip and palate, exhibited a midline levator muscle dehiscence to some extent, which is also consistent with previous literature.[7] (also Nyswonger JC, Perry JL, Kuehn DP, et al, unpublished data, 2016). The participants in the present study all underwent a Wardill-Kilner palatoplasty[15] without radical dissection around the hamulus. Surgical reports did not provide detail about the use of levator muscle overlapping techniques. It is possible that without adequate repositioning of the levator and overlap of the levator muscle fibers in the velar midline, as performed in the double opposing Z-plasy,[16] contraction of the levator muscle may cause the two bundles to pull apart and separate at the midline. Over time, this repeated action may impact the positioning of the two muscle bundles, displacing them more laterally, as seen by the dehiscence among 2 of the participants in the present study. It is also possible that dissection around the hamulus provides greater release of the anterior velar muscles and creates a more normalized placement of the levator muscular sling. Additionally, most all subjects had very thin midline bundles, which likely contributed to our findings. Future studies should investigate the levator morphology as a function of surgery type to determine if overlapping techniques[16-18] produce a more uniform cohesive midline levator sling. Furthermore, it is not known whether overlapping the muscle produces a greater midline bulk more similar to that of the non-cleft anatomy.

Research has shown that the Furlow double opposing Z-plasty is a successful secondary surgical option to improve speech in individuals who have already undergone a primary palate repair, indicating that replacement and overlapping of the levator muscle improves speech outcomes.[18] Due to the small sample size and within group variability in this study, we were not able to assess the degree of contribution point 6 had to the overall measurements of volume, circumference, and diameter. However, it is indisputable that the varying degree of midline deficiency observed in all of the 5 participants played a significant role in the observed morphological differences found in the present study. Longitudinal studies and computational modeling may help us understand the effects of surgical techniques and corresponding outcomes on anatomy.

Previous literature has described the levator muscle as a flattened cylinder that fans out upon entering the intravelar segment.[19-21] Perry et al[9] quantified this shape in adults with normal anatomy using 3D analysis of magnetic resonance images. In the present study, the muscle in the cleft group exhibited a similar shape with the exception of the midline, regardless of whether muscular dehiscence was present. Throughout the extravelar segment (points 1-3), similar measurements were noted between the cleft group in this study and non-cleft anatomy in the literature[9,19-21] with the exception of smaller mean circumference and A-P diameter at the muscle origin (point 1).

Previous studies of non-cleft anatomy observed a broadening of muscle fibers at the insertion of the levator muscle into the velum[22-26] and greater variation in thickness across the intravelar segment (points 4-6).[9] In the present study, consistency in circumference and A-P diameter was observed for cleft anatomy across points 3-5. There was less consistency in S-I diameter for these points, specifically at point 4. The largest difference between cleft and non-cleft anatomy was observed at measurement point 6 (midline of the levator). Perry et al[9] reported the largest mean circumference (23.71 mm) and A-P diameter (9.6 mm) measures to be at midline non-cleft anatomy, whereas the cleft group showed the smallest mean circumference (13.40 mm), A-P diameter (4.86 mm), and S-I diameter (2.08 mm) in this study. Midline difference in the cleft group was not only impacted by the 2 participants with muscular dehiscence, but also the thinness of the muscle across all participants with repaired cleft palate. Overall, variation in thickness and overlap of muscle bundles was observed in the repaired cleft palate group; however, this did not correspond with variations in resonance as expected.

It is important to note that the speech of the 2 individuals with midline dehiscence was within normal limits. Although velopharyngeal dysfunction (VPD) occurs secondary to various changes within the complex VP mechanism, muscle dehiscence has been associated with increased incidence of VPD. Surprisingly, the participant with moderate-severe hypernasality did not display any degree of midline separation but did have a very thin muscle at the velar midline, with circumference and A-P diameter measures greater than one SD below the mean for non-cleft individuals. This finding highlights the importance of investigating other VP variables in addition to the levator variables of the present study. It is well known that VP function is related to the coordination of multiple muscular actions. Additionally, the VP portal dimensions contribute to VP function. Future studies should investigate a potential relationship between 3D levator muscle measures and presence of hypernasality with a larger sample of participants with VPD. Inoyue et al[27] effectively demonstrated through computational modeling that when the levator was not connected at midline, the least amount of velar force was generated, suggesting overlap is a critical feature of levator physiology. In the future, more complex computational modeling including additional VP musculature may be an effective tool to investigate questions related to VP function given variations in the morphology of additional muscles. Since the VP muscles work together as a cohesive mechanism, it is possible that a deficit in the levator muscle could be compensated for by the function of other muscles, resulting in little to no speech difference.

The present study emphasizes the need for long-term surgical follow up after palatoplasty. Kuehn et al[28] proposed questions regarding the fate of the levator muscle following surgery and emphasized the need for pre- and post-surgical MRI evaluation. Given the adult population utilized in this study, these participants were decades past their initial palate repair, and it is impossible to know where the levator was placed during surgery and whether it migrated to a less favorable position. Future studies should employ a longitudinal design to determine levator morphology within the cleft palate population over time to better understand the effects the healing and aging processes have on the muscle.

Limitations

Findings from the present study are most limited by the small sample size (N=15). Future studies should employ a larger sample size in order to make these comparisons of location along the levator between cleft and non-cleft participants. Other limitations of this study include unmatched treatment groups. Perry et al[29] found significant differences between Caucasian men and women across several two-dimensional levator muscle measures. This may explain some of the variability seen within the 3D muscle measures of this study.

Conclusions

Results of this study indicate that adults with repaired cleft palate exhibit decreased levator muscle volume, circumference, and diameter as compared to adults with normal anatomy. This study contributes to the research base to further our understanding into muscle function for abnormal VP control for speech and swallowing, as emphasized by Perry et al.[9] Further MRI studies are needed to assess these differences in levator muscle morphology in a more clinically relevant population, such as children with cleft palate. Detailed analyses should be performed using the 6 landmarks designated by Perry et al.[9] Pre- and post-operative analyses of levator morphology are crucial to understanding how surgery can optimize levator muscle form and function.

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CHAPTER 4

STUDY II

Asymmetry and Positioning of the Levator Veli Palatini Muscle in Children with Repaired Cleft Palate [3]

Abstract

The purpose of this study is to examine the differences in velopharyngeal dimensions as well as levator veli palatini (levator) muscle morphology, positioning, and symmetry of children with repaired cleft palate with velopharyngeal insufficiency (VPI), children with repaired cleft palate with complete velopharyngeal closure (VPC), and children with non-cleft anatomy. In accordance with the local Institutional Review Boards, fifteen English-speaking children ranging in age from 4-8 years were recruited for this study. Ten of the participants had a history of repaired cleft palate, half with documented velopharyngeal insufficiency and the other half with adequate velopharyngeal closure. Five participants with non-cleft anatomy were matched for age from a normative database. The MRI protocol, processing methods, and analysis are consistent with that used in previous literature. In addition, differences between the left and right sides of the levator muscle were calculated as separate variables for angle of origin, muscle length, and muscle thickness at six predefined points along the length of the muscle. Multiple Kruskal-Wallis H tests were run to determine if there were differences in dependent variables between the three groups of participants. Age and facial height were not statistically significant between groups. Regarding measures of velopharyngeal position, median values were statistically significantly different between groups for sagittal angle (p = .031) and effective VP ratio (p =

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[3] **Kotlarek, K. J.**, Pelland, C., Blemker, S. S., Jaskolka, M. S., Fang, X., & Perry, J. L. Asymmetry and Positioning of the Levator Veli Palatini Muscle in Children with Repaired Cleft Palate. *In preparation*.

.013). With respect to the levator muscle, median values were statistically significant for average extravelar length (*p* = .018), thickness at midline (*p* = .021), and thickness between the left and right levator muscle bundles at the point if insertion into the velum (*p* = .037). Remaining measures were not statistically significant. The levator muscle is significantly different among these three groups with respect to symmetry at the point of insertion into the velum. Participants with repaired cleft palate and VPI displayed the greatest degree of asymmetry. Continued evaluation of post-surgical anatomy and short- and long-term outcomes may contribute to a better understanding of surgical impact on velopharyngeal morphology. Future research should control for surgical procedure type to determine the impact of surgery on the levator muscle and surrounding velopharyngeal anatomy.

Introduction

The levator veli palatini (levator) muscle is widely accepted to play the most significant role in velar elevation to close off the passageway between the oral and nasal cavities for speech and swallowing (Hoopes et al., 1969; Dickson and Dickson, 1972; Bell-Berti, 1976; Moon et al., 1994; Perry, 2011). In adult individuals with non-cleft anatomy, there is relatively consistent size, shape, and location of the levator muscle making up the middle one-third of the soft palate, coursing without interruption via cohesive sling (Kuehn & Moon, 2005). However, when there is a cleft of the palate, the levator muscle bundles insert anteriorly, proximal to the posterior aspect of the hard palate, and need to be surgically altered to function property. A primary palatoplasty is completed to achieve complete closure of the cleft in the hard and soft palate and create a physiological mechanism conducive to the development and production of normal speech.

Past research has found variation in morphology among adults with repaired cleft palate. Ha et al. (2007) found variation between four adult men with repaired cleft palate, including varying length and thickness of the levator muscle among the four participants. The distance between origin points, length, and thickness of the levator muscle bundles were smaller than those of non-cleft anatomy reported by Ettema et al., (2002). Kotlarek, Perry, and Fang (2017) compared levator form via total volume, circumference, and diameter measures between cleft and non-cleft adults. Differences in total levator volume as well as circumference and diameter were found, specifically at the point of insertion of the levator muscle into the velum and at the velar midline. Perry et al. (2018) examined differences in velopharyngeal structures between adults with repaired cleft palate and normal resonance and adults without cleft palate, which revealed significant differences in measures of the hard palate, levator muscle, and velopharyngeal portal. This study demonstrated that even in the absence of hypernasality, differences exist between cleft and non-cleft anatomy. It is currently unknown which of these variables are important to developing velopharyngeal closure.

Significant differences between cleft and non-cleft anatomy have also been observed in children. Kuehn et al. (2001) studied two children with cleft palate who underwent a Furlow double-opposing Z-plasty for primary repair of the palate. Post-operatively, both patients exhibited a cohesive midline and improved speech, but one patient still required further surgical intervention due to persisting velopharyngeal dysfunction. Nakamura et al. (2003) studied a group of seven children with repaired cleft palate and persistent velopharyngeal insufficiency (VPI) and found that the velar length was shorter and the pharyngeal length:depth ratio was significantly smaller than those with normal anatomy. Tian et al. (2010a,b,c) studied similar groups to compare 19 participants with repaired cleft palate with and without VPI to a normative control group. They found that the cleft group with VPI had a significantly shorter posterior velar length and longer uvular pharyngeal depth compared to those with velopharyngeal closure (VPC;

Tian et al., 2010b,c). It has been hypothesized that these variables may be required for adequate velopharyngeal closure. When compared to the normative control group, significant differences were present for both cleft groups for measures of levator insertion width, hard palate length, pharyngeal depth (posterior pharyngeal wall, basion, and the 1st cranial vertebra), and maxillary index (Tian et al., 2010b,c). Similar to the adult population with repaired cleft palate, differences exist within the population with cleft palate despite velopharyngeal status.

Additional studies have also looked at function of the velopharyngeal port during speech tasks. Through comparison of rest and sustained phonation tasks of 29 participants, it was found that the cleft group with VPI displayed significantly reduced mobility of the velum and lateral pharyngeal walls even though the levator muscle demonstrated sufficient function during elevation and contraction (Tian et al., 2010a,c). Perry et al. (2016) suggested that significant deviations from normative, non-cleft velopharyngeal measures may attribute to aberrant function for normal resonance.

The levator muscle is widely considered a bilateral, symmetric muscle across the literature. Therefore, several investigations have utilized measurements along one side of the muscle to describe the form of the levator muscle. Although it is likely that the non-cleft population exhibits bilateral muscle bundles of the same form and size, it is unclear whether surgical restoration of the soft palate during primary palatoplasty aims to restore the symmetrical nature of the levator muscle sling. Park et al. (2015) compared the levator muscle of 17 participants with 22q11.2 Deletion Syndrome to nine participants with nonsyndromic submucous cleft palate, indicating a thinner muscle with a greater degree of asymmetry in individuals from this syndromic population. It was proposed that the thinness and asymmetry observed in the syndromic population may lead to suboptimal results after a secondary palatal surgery that depends on levator muscle function (Park et al., 2015). To the best of our knowledge, symmetry of the levator muscle within individuals with repaired cleft palate has not been reported in the literature. It is plausible that, due to surgical intervention, symmetry of the levator muscle may not be established within this population.

The purpose of this study was to examine the two- and three-dimensional differences in velopharyngeal and levator muscle morphology of children with repaired cleft palate compared to children with non-cleft anatomy. It was hypothesized that children with repaired cleft palate, and more so those with VPI, would exhibit greater asymmetry and anterior positioning of the levator muscle. Previous studies have failed to address the impact of levator muscle anatomy on three-dimensional measures, such as levator muscle volume and thickness, which has been found to be significantly different between cleft and non-cleft adults (Kotlarek et al., 2017). Furthermore, previous investigations regarding comparisons between cleft and non-cleft children have not addressed symmetrical comparisons between right and left muscle bundles of the levator muscle. This is of specific interest due to the laterality of some forms of clefting and the effect of surgery on the restoration of the levator muscle.

Methods

Participants

In accordance with the local Institutional Review Boards, fifteen English-speaking children ranging in age from 4-8 years (Mean age = 6.24 years, SD = 1.1 years) were recruited for this study. Ten of the participants had a history of repaired cleft palate, half with documented velopharyngeal insufficiency (VPI; Mean age = 6.75 years, SD = 1.3 years) and the other half with adequate velopharyngeal closure (VPC; Mean age = 5.77 years, SD = .7 years). Five participants with non-cleft anatomy were matched for age from a normative database (Mean age

= 6.21 years, SD = 1.3 years). Participants were not matched for sex or race due to the lack of sexual dimorphism regarding velopharyngeal variables in children within this age range (Perry et al., 2018). Participant details are reported in Table 3. Within the VPI group, two had bilateral complete cleft lip and palate and three had unilateral left cleft lip and palate; the VPC group contained two participants with bilateral complete cleft lip and palate, one with unilateral left cleft lip and palate, and two with cleft palate only. All of the participants with cleft palate underwent primary palatoplasty between the ages of 6-18 months. Surgical repair of the palate was completed by different surgeons using either a V-Y pushback (7 participants) or a Furlow double-opposing Z-plasty (3 participants). None of the participants had received secondary palate repair at the time of MRI study. For participants with cleft palate, velopharyngeal status at the time of scanning (VPC or VPI group) was determined through information provided in the craniofacial team report. For the purpose of this study, the VPI group was defined as those participants who were referred for secondary surgical management by the craniofacial team. All participants within the normative control group had normal speech. In both instances, perceptual resonance evaluations were completed by a speech-language pathologist with a minimum of five years' experience in craniofacial speech evaluations.

Table 3. Description of participant groups in the present study.

Group	**n**	**Mean age (y)**	**SD (y)**
Non-cleft	5	6.21	1.3
VPC	5	5.77	0.7
VPI	5	6.75	1.3
Total	***15***	***6.24***	***1.1***

Imaging Protocol

Five different MRI scanners were used to scan the participants for this study because the participants were recruited in different geographic regions. MRI protocols were designed to produce similar images between scanners by establishing sequences across all scanners that yielded a similar in-plane isotropic resolution of .8. Reliability between scanners has been reported in previous literature (Perry et al., 2018). The imaging protocol was consistent with that used in previous MRI investigations of the velopharyngeal muscles (Perry, Kuehn, & Sutton, 2013). All participants were scanned using a head coil while lying in the supine position. Children were prepared for the scan following a child-friendly protocol without the use of sedation (Kollara & Perry, 2014).

Image Analysis

The MRI processing methods are consistent with that used in previous literature (Perry & Kuehn, 2007, Perry & Kuehn, 2009; Perry, Kuehn, & Sutton, 2011; Perry, Kuehn, & Sutton, 2013). Specifically, raw magnetic resonance images were transferred into Thermo Scientific™ Amira™ Software (Thermo Fisher Scientific, Waltham, MA, US), which includes a native Digital Imaging and Communications in Medicine (DICOM) support program to ensure that anatomical geometry is maintained. The entire dataset was resampled from the 3D anatomical scan to obtain the oblique coronal image for the full sling of the levator muscle to be visualized (Figure 10). For volumetric measures, the levator muscle fibers were defined by manual segmentation of successive oblique coronal images, from which a voxel set was created, and volume was calculated (Kotlarek et al., 2017). Two-dimensional measures of interest were taken from both the mid-sagittal and central-most oblique-coronal image planes. In addition, thickness points were taken at six designated points along both sides of the length of the levator muscle, as described by Perry et al., 2013 (Figure 11). All definitions of measures and terms are detailed in Table 4. Averages between the left and right side were calculated within the same participant. Symmetry measures were calculated using the absolute value of the difference between the right and left sides. Both average and symmetry measures were completed on the following measures: Angle of origin, levator length, extravelar length, intravelar length, and muscle thickness at points 1-5.

Figure 10. A midsagittal image is shown with the white line showing the oblique coronal image plane.

Figure 11. The levator muscle shown from origin to insertion from the oblique coronal image plane. Points 1-6 on the left and right are shown, according to Perry et al., 2013.

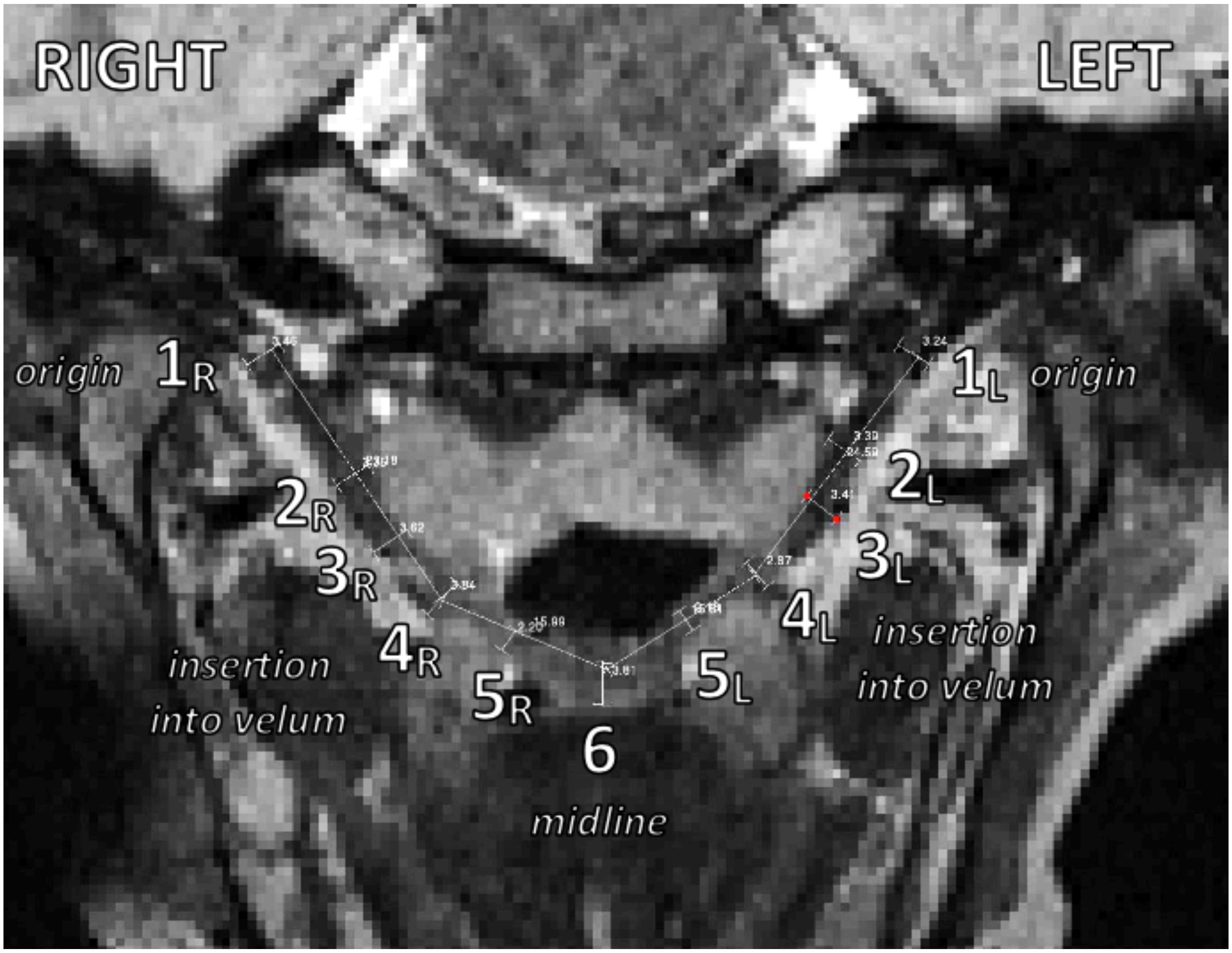

Table 4. List of measurements and corresponding definitions.

Velopharyngeal Variables	
Pharyngeal depth	Linear distance (mm) between the posterior nasal spine and posterior pharyngeal wall (or adenoid) at the level of the palatal plane as seen on the midsagittal image
Velar thickness	Linear distance (mm) from the oral to the nasal surface of the velum at the thickest point from the midsagittal image
Velar length	Curvilinear distance (mm) from the posterior nasal spine to the tip of the uvula
Effective velar length	Linear distance (mm) from the posterior nasal spine to the middle of the levator muscle where it inserts into the body of the velum as seen on the midsagittal image
Muscle pharyngeal depth	Linear distance (mm) from the middle of the levator muscle where it inserts into the body of the velum to the posterior pharyngeal wall (or adenoid) parallel to the palatal plane as seen on the midsagittal image
Velopharyngeal ratio	Velar length divided by pharyngeal depth
Effective velopharyngeal ratio	Effective velar length divided by pharyngeal depth
Sagittal angle	Internal angle (degrees) between the plane of the levator muscle and the line coursing through the anterior tubercle of the 3rd and 4th cervical vertebrae as seen on the midsagittal image
Levator Muscle Variables	
Origin to origin distance	Linear distance (mm) between the two points of origin for the right and left levator muscle bundles as seen on the oblique coronal image
Levator length	Curvilinear distance (mm) of the levator veli palatini muscle from the base of the skull (origin) through the midline of the muscle bundle as seen on the oblique coronal image
Angle of origin	Angle (degrees) created by the line connecting the two temporal origins of the levator muscle and the line coursing through the levator muscle bundles as seen on the oblique coronal image
Extravelar segment length	Curvilinear distance (mm) of the levator veli palatini muscle from base of the skull (origin) through the midline of the muscle bundle to the point where the muscle inserts into the body of the velum as seen on the oblique coronal image.
Intravelar segment length	Curvilinear distance (mm) of the levator veli palatini muscle from the point where the muscle inserts into the body of the velum to midline as seen on the oblique coronal image
Velar insertion distance	Linear distance (mm) between the locations where the levator bundles insert into the body of the velum as seen on the midsagittal image
Total volume	The total volume (mm^3) of the levator muscle calculated from a voxel set of consecutive oblique coronal images
Muscle thickness	Side-to-side (medial-lateral for points 1-3; superior-inferior for points 4-6) diameter of the levator muscle as seen on the oblique coronal image

Statistical Analysis

Due to the small sample size and non-normal distribution of data, nonparametric statistical analyses were adopted for comparing measures between the participant groups. All assumptions were adequately met for the Kruskal-Wallis H test, including a continuous dependent variable, one independent variable consisting of two or more categorical, independent groups, and independence of observations. Multiple Kruskal-Wallis H tests were conducted using IBM SPSS 24.0 (IBM Corp, Aramonk, NY) to determine if there were differences in the aforementioned variables among groups that differed in their velopharyngeal status: the “non-cleft” (n = 5), “cleft with VPC” (n = 5), and “cleft with VPI” (n = 5) groups. Median values were also provided. Pairwise comparisons were conducted with Bonferroni correction for multiple comparisons, and adjusted *p*-values are presented.

An intraclass correlation was used to assess inter- and intra-rater reliability. Reliability was completed on 100% of participants using angle measures due to angles having the lowest reliability in previously reported MR imaging studies of the velopharyngeal mechanism. Inter-rater reliability ranged from r = .839 to .964, which was calculated using separate measurements competed by two researchers with experience in 3D MRI data analyses. Intra-rater reliability was completed on the same set of angle measures two weeks later. Intra-rater reliability ranged from r = .824 to .997 for these selected measures.

Results

Multiple Kruskal-Wallis H tests were run to determine if there were differences in variables among the three groups of participants. Participant age was not significantly different (*p* = .623) among the non-cleft (Mean = 6.21 years, Median = 5.92 years), VPI (Mean = 6.75 years, Median = 7.23 years), and VPC (Mean = 5.77 years, Median = 5.89 years) groups. Facial height was also not significantly different (*p* = .093) among the non-cleft (Mean = 91.08 mm, Median = 93.16 mm), VPI (Mean = 100.91 mm, Median = 99.39 mm), and VPC (Mean = 92.38 mm, Median = 88.92 mm) groups. Due to the small sample size and the result that age and facial height were not statistically significant among groups, the influence of growth was not included in further analysis. Regarding measure of velopharyngeal position, median values were significantly different across groups for sagittal angle ($\chi^2(2) = 6.980$, $p = .031$). Median sagittal angle measures increased from non-cleft (50.2°), to cleft with VPC (57.8°), to cleft with VPI (69.7°) groups. Post hoc analysis revealed a significant difference in sagittal angle between the non-cleft (mean rank = 4.60) and cleft with VPI (mean rank = 12.00; *p* = .027) groups but not between any other group combination. Median values were also significantly different for effective velopharyngeal ratio ($\chi^2(2) = 8.720$, $p = .013$), increasing from cleft with VPI (.18), to non-cleft (.65), to cleft with VPC (.72) groups. Post hoc analysis revealed a statistically significant difference in effective velopharyngeal ratio between the cleft with VPI (mean rank = 3.20) and non-cleft (mean rank = 10.00; *p* = .049) group as well as the cleft with VPI and cleft with VPC (mean rank = 10.80; *p* = .022) groups.

With respect to the levator muscle, median values were significantly different for extravelar length ($\chi^2(2) = 7.980$, $p = .018$). Median extravelar length increased from cleft with VPI (25.30 mm), to non-cleft (25.98 mm), to cleft with VPC (31.85 mm) groups. Post hoc analysis revealed a statistically significant difference in extravelar length between the cleft with VPC (mean rank = 12.40) and cleft with VPI (mean rank = 4.60; *p* = .017) groups but not between any other group combination. Median values were also significantly different for levator muscle thickness at midline ($\chi^2(2) = 7.692$, $p = .021$), increasing from cleft with VPI (1.32 mm), to cleft with VPC (3.16 mm), to non-cleft (3.81 mm) groups. Post hoc analysis revealed a statistically significant difference in levator muscle thickness at midline between the non-cleft (mean rank = 12.10) and cleft with VPI (mean rank = 4.30; $p = .017$) groups but not between any other group combination. Median values were significantly different for the difference between the thickness between the left and right levator muscle bundles at the point if insertion into the velum ($\chi^2(2) = 6.620$, $p = .037$), increasing from non-cleft (.11 mm), to cleft with VPI (1.25), to cleft with VPC (1.31 mm) groups. Post hoc analysis revealed no significant pairwise comparisons for the difference in thickness of the right and left levator muscle bundles at the point of insertion into the velum. All significant measures are shown in Table 5. Remaining measures were not found to be significantly different among groups.

Table 5. Significant results of the Kruskal-Wallis H-test and associated pairwise comparisons are shown in the table below. * indicates significant pairwise comparison, $p < .05$; Diff = absolute value of left muscle thickness subtracted from right muscle thickness

Variable (units)	**Medians**	**H-test**		**Pairwise**		
		χ^2	***P*-value**	**Mean Ranks**		***P*-value**
Sagittal Angle	VPI: 69.7	6.980	.031	VPI: 12.00	Non: 4.60	.027*
	VPC: 57.8			VPC: 7.40	VPI: 12.00	.312
	Non: 50.2			Non: 4.60	VPC: 7.40	.967
Effective VP Ratio	VPI: .18	8.720	.013	VPI: 3.20	Non: 10.00	.049*
	VPC: .72			VPC: 10.80	VPI: 3.20	.022*
	Non: .65			Non: 10.00	VPC: 10.80	1.00
Average Extravelar Length	VPI: 25.30	7.980	.018	VPI: 4.60	Non: 7.00	1.000
	VPC: 31.85			VPC: 12.40	VPI: 4.60	.017*
	Non: 25.99			Non: 7.00	VPC: 12.40	.169
Midline Levator Thickness	VPI: 1.32	7.692	.021	VPI: 4.30	Non: 12.10	.017*
	VPC: 3.16			VPC: 7.60	VPI: 4.30	.727
	Non: 3.81			Non: 12.10	VPC: 7.60	.333
Diff Levator Thickness at Insertion	VPI: 1.25	6.620	.037	VPI: 10.00	Non: 3.80	.085
	VPC: 1.31			VPC: 10.20	VPI: 10.00	1.000
	Non: .11			Non: 3.80	VPC: 10.20	.071

Discussion

This study examined whether differences existed in the symmetry, morphology, and position of the levator muscle among participants with repaired cleft palate and VPC, participants with repaired cleft palate and VPI, and non-cleft controls. Significant differences among the three groups were found for variables of sagittal angle, effective VP ratio, extravelar length, midline levator thickness, and the difference in thickness of the levator muscle bundles at the point of levator insertion into the body of the velum.

Comparison Between Cleft and Non-Cleft Groups

Tian and colleagues (2010b,c) found significant differences were present for both cleft groups for measures of levator insertion width, hard palate length, pharyngeal depth (PPW, basion, and the 1st cranial vertebra), and maxillary index when compared to the normative control group (Tian et al., 2010b,c). The present study found significant differences between cleft and non-cleft (VPI or VPC) groups with respect to sagittal angle, levator muscle thickness and midline, and symmetry at the point of levator insertion into the velum. Levator insertion width (velar insertion distance) was not found to be different among groups in this study, which may be due to individual variability and an effect of the low sample size in both this study as well as the Tian et al. (2010b,c) studies.

Median values were statistically significantly different between groups for sagittal angle, the cleft with VPI group having the largest sagittal angle. Post hoc analysis revealed significant differences in sagittal angle between the non-cleft and cleft with VPI groups. Although this specific measure has not been employed to compare children with cleft palate, it has been reported in normative measures of the velopharynx in children (Perry et al., 2018). The more obtuse the angle measure, the more horizontal the levator is positioned, which gives the muscle a disadvantageous pull on the body of the velum (Perry et al. 2013). In addition, sagittal angle could also be influenced by changes to the point of origin or insertion of the levator muscle, such as anteriorly-positioned levator muscle bundles or cranial base variations. Given that the median sagittal angle of the VPI group was the greatest in combination with a reduced effective velar length, it would be probable that the levator muscle is positioned anteriorly within this group. Such anterior levator fibers result in an unfavorable biomechanical lever system that may result in a velopharyngeal gap.

Levator muscle thickness at midline was significant between groups. The group with VPI had the lowest median midline levator thickness. Two of these participants had midline separation of the levator muscle bundles, showing a thickness of zero for this measure. Post hoc analysis revealed significant differences non-cleft and cleft with VPI, indicating midline levator muscle thickness may be indicative of velopharyngeal function. Many current surgical interventions aim to restore the levator muscle sling during primary palatoplasty with varying degrees of overlap. Future research should control for muscle overlap to determine if there is an optimal percentage of overlap to maintain muscle continuity and optimize function.

Asymmetry was observed at the point of levator insertion into the velum. Median values were significant for the difference between the thickness between the left and right levator muscle bundles at the point if insertion into the velum, with the smallest amount of asymmetry observed in the non-cleft group. Asymmetry between the VPC and VPI groups was 0.06 mm different and likely not relevant to velopharyngeal status. Future comparisons should be made to syndromic populations, such as 22q11.2 deletion syndrome, to determine if there is a greater degree of asymmetry relative to velopharyngeal status. Future research should also compare dynamic speech data via nasendoscopy or dynamic MRI to determine if this muscular asymmetry is functional.

Comparison Between VPI and VPC Cleft Groups

Tian et al. (2010b,c) studied similar groups to that of the present study and found only two significant differences between the VPI and VPC groups. Specifically, the cleft group with VPI had a significantly shorter posterior velar length and longer uvular pharyngeal depth compared to those with VPC (Tian et al., 2010b,c). VP ratio and effective VP ratio were not found to be significantly different between these two groups, which led to the conclusion that the posterior velum may play an important role in VP function for speech. In the present study, differences in the VPI and VPC groups were found for variables of extravelar length and effective VP ratio.

Extravelar length was significantly different across the three study groups in this study. Significant differences were noted between the VPI and VPC groups, with the greatest extravelar length noted for the VPC group. To the best of our knowledge, this difference relative to VP function has not been reported in previous literature. Tian et al., (2010b,c) did not find a significant difference in the levator muscle between these groups; however, extravelar length was not measured separately from the entire levator muscle as it was in the present study. It has previously been thought that the extravelar portion of the levator muscle plays an important role in velopharyngeal function, as it has the greatest potential for pulling the velum upward (Perry, et al., 2014). Due to the lower variability observed within the extravelar segment (compared to the intravelar segment) of the levator muscle, the extravelar segment may play an important role in VP function (Perry et al. 2014).

Median values were also statistically significant for effective velopharyngeal ratio in the present study, cleft with VPI having a drastically smaller ratio and more disadvantageous than non-cleft or cleft with VPC groups. Post hoc analysis revealed significant differences in effective velopharyngeal ratio between the VPI group compared to both other groups. This demonstrates that effective velopharyngeal ratio highly relevant to velopharyngeal closure. Additional investigations should determine if effective VP ratio is able to predict velopharyngeal closure. Tian and colleagues (2010b,c) reported the VPI group had a significantly shorter posterior velar length and longer uvular pharyngeal depth compared to those with VPC, however, effective VP ratio was not significant. Although also not significant, a greater pharyngeal depth (posterior nasal spine to posterior pharyngeal wall) was noted for both the VPI and VPC groups, which may have contributed to a longer effective velar segment and more normalized effective VP ratio in the Tian et al (2010b,c) studies. Type of surgical intervention may be responsible for differences observed in this study.

Surgical differences. Differences in surgical type as well as operating surgeon were not utilized as covariates within the present study due to the low sample size. Participants were consecutively enrolled, which did not allow us to limit the population to a single surgeon. Four of the five participants within the VPI group underwent a V-Y pushback palatoplasty. Within the VPC group, three participants underwent a Furlow double-opposing Z-plasty while two had a V-Y pushback palatoplasty. Although the surgical methods of the Z-plasty may logically lead to more asymmetry of the levator muscle, the participants who underwent a V-Y pushback showed greater difference in thickness at the point of insertion into the velum. In addition, two of the participants in the present study (one VPC, one VPI) who showed midline dehiscence of the levator muscle bundles (midline thickness = 0 mm) underwent a V-Y pushback. Future research should include surgical variables within the statistical analysis to determine if certain interventions yield more advantageous post-operative anatomy.

Limitations

Generalization of these results is restricted based on the limited sample size employed by this study. Control for participant race, surgical type, and operating surgeon were not considered in this study due to the limited sample size and should be controlled in future investigations.

Future Directions

Future research should compare children and adults with repaired cleft palate and differing velopharyngeal status using a larger sample size. Much research has been published comparing individuals with repaired cleft palate to their non-cleft peers; however, research has shown that individuals with repaired cleft palate that achieve velopharyngeal closure and typical speech production have asymptomatic differences in levator and velopharyngeal variables. In addition, a larger sample size would allow for comparison across specific surgical types to determine how the surgical procedure impacts the velopharyngeal anatomy. Further research in this area may enable surgery selection to be based on individual anatomy and reduce overall need for secondary intervention for VPI.

Conclusion

The levator muscle is significantly different among these three groups with respect to symmetry at the point of insertion into the velum. Participants with repaired cleft palate and VPI displayed the greatest degree of asymmetry. Continued evaluation of post-surgical anatomy and short- and long-term outcomes may contribute to a better understanding of surgical impact on velopharyngeal morphology. Future research should control for surgical procedure type to determine the impact of surgery on the levator muscle and surrounding velopharyngeal anatomy.

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CHAPTER 5

STUDY III

Investigation of the Anatomical and Physiological Changes Following the Use of a Pedicled Buccal Fat Pad Graft During Primary Palatoplasty

Abstract

Purpose: The purpose of this study was to use MRI to examine the surgical impact of the pedicled buccal fat pad (BFP) graft on velar composition and velopharyngeal anatomy after it is placed at the palatine aponeurosis at the time of primary palate repair. Methods: Fifteen English-speaking children ranging in age from 3-7 years were recruited for this study as part of three groups: non-cleft, traditional palatoplasty, and palatoplasty with BFP graft placement. The MRI protocol, processing methods, and analysis were consistent with that used in previous investigations of the velopharynx using MRI. Variables of sagittal angle, velar thickness, effective velar length, velar stretch, and percentages of fat and muscle within the velum were analyzed. Results: Group comparisons of velar thickness ($p = .011$), effective velar length ($p = .018$), and percentage of fat within the velum at midline ($p = .005$), left paramedian ($p = .028$), and right paramedian ($p = .005$) were significantly different among groups. Conclusions: Additional research employing a larger sample size should be completed to evaluate the outcomes compared to those not receiving a pedicled BFP graft, as well as cross-sectional data across the lifespan.

Introduction

Orofacial clefting is one of the most common birth defects. Children born with a cleft palate typically undergo primary palatoplasty between 6-12 months of age. Currently, there are various surgical techniques used during primary palatoplasty, which differ between centers and among surgeons (Agrawal, 2009). Current literature suggests that positive outcomes are only apparent approximately 70-80% of the time regardless of the type of procedure used (Marsh, Grames, & Holtman, 1989; Moore, Lawrence, Ptak, & Trier, 1988; Musgrave & Bremner, 1960; Phua & de Chalain, 2008; Sullivan, Marrinan, LaBrie, Rogers, & Mulliken, 2009). It is estimated that 25-37% of children with a repaired cleft palate need a second surgery to eliminate the presence of hypernasal speech (Bicknell et al., 2002; Lithovius et al., 2014). Hypernasal speech is a common symptom of VPD among children with repaired cleft palate.

Research has sought to determine which anatomical markers are predictive of VPD. Reduced palate length and increased pharyngeal depth have been commonly associated with VPD (D’Antonio et al., 2000; Randall et al., 2000). These measures form the velar depth:length ratio, which is equal to 0.68 in the normative population (Subtelny, 1957). The depth:length ratio is greater in individuals with repaired cleft palate, producing a velopharyngeal gap causing hypernasal speech (D’Antonio et al., 2000; Satoh et al., 2005). Velar stretch, or the ability of the velum to increase in intrinsic length from rest to elevation, has also been linked to adequate velopharyngeal closure (Pruzansky & Mason, 1969). It has been proposed that limited velar stretch in individuals with cleft palate is due to resistance and rigidity of velar scar tissue (Tian et al., 2010b). Individuals with repaired cleft palate have been shown to display decreased levator veli palatini (levator) muscle volume compared to non-cleft individuals (Ha et al., 2007; Kotlarek et al., 2017; Tian et al., 2010a). Research in computational modeling has indicated that the musculus uvulae's function as a velar extensor may be crucial in providing adequate length for velopharyngeal closure (Inouye et al., 2016). The musculus uvulae is a midline velar muscle thought to be responsible for adding bulk to the velum and creating a tight seal between the velum and posterior pharyngeal wall during VP closure (Azzam & Kuehn, 1977). In individuals with cleft palate, the musculus uvulae has been described as reduced or absent (Huang et al., 1997; Pigott et al., 1969). The musculus uvulae nearly triples the midline velopharyngeal contact length as a space-occupying structure (Inouye et al., 2016). It has been proposed that in the case of its absence, autologous fat, muscle, or scar tissue build up may add velar stiffness and could be used in place of the musculus uvulae to eliminate the velar midline defect (Inouye et al., 2016).

The palatine aponeurosis in non-cleft anatomy also has implications for lengthening the palate and increasing midline velar mass to support velopharyngeal closure. The palatine aponeurosis is a tough, tendinous sheath existing in the anterior two-thirds of the soft palate that transmits muscle forces. In individuals with cleft palate, this tissue has been described as absent, dislocated, or abnormal (Koch et al., 1998; Kriens, 1971). Although some groups have suggested the unfolding and repositioning of the aponeurosis is important to reestablishing length and function of the palate (Sommerlad, 2003), few surgical interventions mention restoration or management of this tissue. Therefore, when the levator sling is restored at midline during primary palatoplasty, there is likely an area of absent space covered by oral and nasal mucosa at the palatine aponeurosis. It has been hypothesized that this denude region causes the surgically retropositioned levator sling to migrate anteriorly back to the original unfavorable position (Zhang et al., 2010). Such anterior levator fibers result in an unfavorable biomechanical lever system that results in a velopharyngeal gap.

The BFP is a bilateral, encapsulated mass located between the buccinator and masseter muscles of the cheek. The BFP graft (or flap) has been a well-documented technique for closure of oral defects, including literature pertaining specifically to the repair of cleft palate fistulae (Ashtani et al., 2011; Egyedi, 1977; Grobe et al., 2011; Habib & Medra, 2016; Hanazawa et al., 1995; Jain et al., 2012). Literature has presented the utilization of the BFP in primary palatoplasty (Kim, 2001; Levi et al., 2009; Pappachan & Vasant, 2008; Pinto & Debnath, 2007; Yamaguchi et al., 2016; Zhang, et al. 2010). Levi and colleagues (2009) hypothesized this technique results in an increase in vascularized tissue at the posterior hard palate. In such, it was expected that this increase in volume and vascularity would prevent wound contracture, thus maintaining a longer velar position and optimizing maxillary growth. Pappachan and Vasant (2008) also claimed this technique results in an increase in velar lengthening. Increased palate length has been shown to be indicative of successful speech outcomes, emphasizing the importance of adequate palatal length on normal velopharyngeal function for speech (D'Antonio et al., 2000; Randall et al., 2000). It has been suggested that the use of a pedicled BFP graft during primary palatoplasty may improve maxillary growth while maintaining a favorable depth:length ratio for VP closure (Zhang et al., 2015). These hypotheses regarding velar lengthening, decrease in velar scar composition, and thus improved velar function have not been systematically examined and compared to children with cleft palate not receiving BFP nor children without cleft palate. Additionally, these studies have been limited to small case reports with no assessments during speech production. The effects of pedicled BFP graft placement at the time of primary palatoplasty on velopharyngeal anatomy and physiology are currently unknown.

MRI is the only imaging modality that allows visualization of the internal musculature *in vivo*. Computerized tomography is an excellent imaging method for bone, however, it cannot be used to visualize musculature to the same degree in which MRI can. Kuehn et al. (2004) demonstrated the clinical utility of comparisons between pre- and postsurgical MRI scans. Studies have previously examined the levator muscle in adults with normal anatomy (Bae et al., 2011b; Ettema et al., 2002; Perry, 2011; Perry et al., 2013a; Tian & Redett, 2009), adults with cleft palate anatomy (Ha et al., 2007; Kotlarek et al., 2017), children with cleft and non-cleft anatomy (Kollara & Perry, 2014; Tian et al., 2010a, 2010b), and infants with cleft and non-cleft anatomy (Kuehn et al., 2004; Perry et al., 2011; Schenck et al., 2016). These MRI studies demonstrate the value of using MRI and its potential clinical utility to improve postsurgical speech outcomes. Knowledge of these outcomes provides important insight into anatomical variations that may produce more favorable dimensions for adequate velopharyngeal closure.

The purpose of this study was to use non-sedated MRI to determine whether BFP graft placement at the palatine aponeurosis during the time of primary palatoplasty creates more favorable velopharyngeal dimensions for adequate closure. We compared measures of anatomical parameters, physiological function, and tissue composition among the three participant groups collected as part of this project. Data from this study provided quantitative details about the anatomic and physiologic impact of the use of BFP during primary palatoplasty.

Methods

Participant Demographics

Fifteen children between the ages of 3-7 years of age were enrolled in this study. Five of these children received primary palatoplasty with a pedicled BFP graft by the same surgeon (Dr. Michael Jaskolka). All children were free of syndromes or musculoskeletal disorders. In addition, five children with repaired cleft palate without a pedicled BFP graft and five children with normal anatomy were also enrolled. Participant demographics are shown in Table 6.

Table 6. Participant distribution among groups is shown.

N = 15	Group	Description
5	BFP	Palatoplasty with BFP placement
5	Cleft	Traditional palatoplasty
5	Norm	Normative control group

Inclusion criteria. To be enrolled in either of the two groups with cleft palate, children had a diagnosis of either bilateral cleft lip and palate, unilateral cleft lip and palate, or cleft palate only and were between 3-7 years of age. Children must have received their primary palate repair between 8-14 months of age to control for the effect of age of primary palate repair on speech. Children were consecutively enrolled, thus children presented with varying degrees of hypernasality.

Exclusion criteria. Children who presented with the following were excluded: palatal fistula (except for alveolar fistulae), neurologic impairment, musculoskeletal disorder, permanent orthodontic device (due to metal interference with MRI), learning disability, secondary surgery for resonance (e.g., pharyngoplasty, pharyngeal flap, palate re-repair), or permanent bilateral hearing loss.

Justification for age selection. The range of 3-7 years of age was selected because it represents the typical age of speech acquisition for children with cleft palate. The operating surgeon has also been at the clinical site for six years, so this age range allowed for control of the operating surgeon between participants.

Justification of sample size. Due to the novelty of this study, a sample size of 15 (five participants per group) was determined to be acceptable for this type of work. Although the sample size was small, it does allow for group comparisons when utilizing nonparametric statistical analyses. The principal investigator (PI) acknowledges specific limitations which are acceptable given the recruitment and retention limitations of this low incidence, pediatric population. This study is the first preliminary report of MRI being used to evaluate this surgical technique.

Recruitment. Participants were recruited from New Hanover Regional Medical Center Cleft and Craniofacial Team as well as the operating surgeon's former clinical site, Charleston Area Medical Center Cleft and Craniofacial Center.

Participants were identified through use of a flyer that described the study goals and details regarding participant involvement. The PI emphasized that the decision to participate in this research had no impact (either good or bad) in their treatment at their hospital and cleft palate team. These flyers were given to each patient seen at regularly scheduled cleft teams that met the inclusion/exclusion criteria. Each child who was followed by the cleft palate craniofacial team at each site returned yearly (at least once a year) for a follow-up appointment. Therefore, this method of recruitment was very successful. If a parent/caregiver expressed an interest in the study, a researcher from the site called the parent and discuss by phone the risks, benefits, and procedures of the study. We also recruited from the local community via flyers placed throughout the community and followed the same informed consent process.

Experimental Procedure

This study utilized a prospective study design for the assessment of anatomical and physiological variables. Post-operative MRI data were collected at a single time point.

Surgical methods of the pedicled buccal fat pad graft group. During primary repair of the cleft palate, all repairs involving pedicled BFP graft placement at the palatine aponeurosis were completed by the same craniofacial surgeon (Dr. Michael Jaskolka) of New Hanover Regional Medical Center. Repairs without a pedicled BFP graft were completed by the same surgeon or an alternative craniofacial surgeon, depending on the specific participant.

Incision of the cleft margin split the oral and nasal mucosa and carried anteriorly and continued through the periosteum of the hard palate. Lateral incisions carried to the anterior cleft margins parallel to the alveolar ridge were also made and carried posteriorly around the posterior alveolus and extended down the raphe. Anterior subperiosteal dissection was completed to identify the neurovascular bundle and the edges of the hard palate. Dissection carried lateral and posterior to the neurovascular bundle and onto the nasal surface of the hard palate, ensuring elevation and release of the mucosa. Bilateral oral mucosal flaps were incised from the base of the uvula toward the tip of the hamulus, elevated in the submucoglandular plane, and incised posteriorly to the hard palate toward the tip of the hamulus before additional underlying dissection of the muscle from the back of the hard palate and division of the tensor tendon was completed. The releasing incisions were bluntly dissected. The nasal layer of the hard palate was then closed, and the uvula was reconstructed. The remainder of the nasal surface was closed. A pedicled BFP graft was dissected (unilaterally or bilaterally), brought through a tension-free tunnel behind the neurovascular bundle, and inset into the posterior border of the hard palate. The oral side was inset, and the flaps were closed in the midline. Several horizontal mattress sutures were placed at the junction of the hard and soft palate. The remainder of the oral side was closed without additional tension.

Magnetic resonance imaging. This study implemented the use of a non-sedated, child-friendly protocol previously published by Kollara and Perry (2014). The PI of this study contacted parents via phone call to review the study steps and answer any initial questions. Participants were emailed a coloring book of a child completing an MRI study, which describes the MRI process in child-friendly verbiage with pictures. Parents/Guardians were encouraged to talk to their children about the MRI prior to the scheduled study date while they read and colored the book together. On the day of the MRI, written consent was obtained from the participant's legal guardian, and written assent was obtained from the participant if they were of age, per Institutional Review Board requirements. The PI reviewed the MRI steps with the participant and their legal guardian. Concepts, such as the importance of remaining still while the MRI was taking place and the loud noise that occurs, were discussed again with the participants and their parent/guardian. The PI answered any additional questions that the participants or their parents/guardians had. Each participant (and guardian, if applicable) completed a safety screening administered by the MRI technologist at their corresponding MRI site. Participants were provided with ear plugs and headphones, and their head was secured with towels to fit snugly in the headcoil. Participants were instructed on the use of the "panic button," which they had with them at all times during the MRI. The participants were able to listen to music or watch a movie while the MRI was taking place.

Three MRI scanners were used to implement this study due to geographical distance within the recruitment area. New Hanover Regional Medical Center and Vidant Medical Center were equipped with a 1.5 Tesla Siemens MRI machine and Wake Forest School of Medicine was equipped with a 3 Tesla Siemens MRI machine (Erlangen Germany). Reliability has previously been established between 1.5 Tesla and 3 Tesla MRI machines by our group (Perry et al., 2018). Participants were not sedated. Children were imaged using a high resolution, T2-weighted turbo-spin-echo three-dimensional anatomical scan called SPACE to acquire a large field of view covering the oropharyngeal anatomy (25.6 x 19.2 x 15.5 cm) with 0.8 mm isotropic resolution and an acquisition time of slightly less than 5 minutes (4 min 52 s). Head rotation was minimized by use of cushions around the head with an elastic strap attached to each side of the head coil passing over the glabella. In addition, a speech MRI during sustained phonation was also taken. A midsagittal two-dimensional scan was obtained during production of the sounds /s/ and /i/. These two-dimensional scans took 7.8 s each and allowed for the velum to be viewed in an elevated position. These imaging sequences described previously (Bae et al., 2011b; Perry et al., 2013b) provided a data set of the structures of interest.

Imaging analysis. Image processing was completed using Thermo Scientific™ Amira™ Software (Thermo Fisher Scientific, Waltham, MA, US). This program has a native Digital Imaging and Communication in Medicine (DICOM) support program which preserves the original anatomical geometry. Measures are defined in Table 7. Measures of effective velar length, sagittal angle, velar thickness, and velar stretch were taken from the midsagittal image plane. Velar stretch was calculated by taking the distance from the posterior hard palate to the velar knee during sustained phonation and subtracting the same distance during the rest position, as described by Tian et al. (2010a). Tissue composition was obtained through segmentation of three anterior-posterior cross-sectional areas of the velum: midline, left paramedian, and right paramedian. Left and right paramedian planes were defined as the point half way between the midline and the respective hamulus on either side. Percentages of muscle and fat within those three slices were obtained for all participants.

The PI measured all data using this software. One angle measure and one linear measure were re-measured by the PI and the research mentor (Perry) to establish intra- and interrater reliability, respectively. The research mentor (Perry) was blinded to the participant group prior to measuring to reduce bias.

Table 7. Variable definitions, imaging plane, and main peer-reviewed reference from which it was taken.

Measure	**Definition**	**Plane of Reference**	**Reference**
Sagittal angle (°)	Curvilinear distance between the posterior border of the hard palate and the center of the uvula at rest	Mid-sagittal	Mason & Perry (2016)
Velar thickness (mm)	Distance from the velar knee to the velar dimple	Mid-sagittal	Perry (2011)
Effective velar length (mm)	Linear distance between the posterior nasal spine and the levator muscle bundle	Mid-sagittal with oblique coronal plane overlaid	Tian et al. (2010)
Velar tissue composition (fat, muscle; %)	Percentage of muscle or fat tissue to other tissue within the body of the velum using cross-sectional areas	Sagittal	Bae, Kuehn, & Sutton (2016)
Velar stretch (mm)	Calculated by the following formula: Velar length$_{rest}$ - velar length$_{phonation}$)	Mid-sagittal	Tian et al. (2010)

Statistical analysis. All statistical analyses were conducted using IBM SPSS 24.0 (IBM Corp, Aramonk, NY). All analyses were designed to quantify differences in anatomical and physiological variables across the three groups. Nonparametric statistical analyses were utilized for comparing measures between the participant groups primarily due to the small sample size and the non-normal distribution of data. All assumptions were adequately met for the Kruskal-Wallis H test, including a continuous dependent variable, one independent variable consisting of two or more categorical, independent groups, and independence of observations. If applicable, pairwise comparisons were conducted with Bonferroni correction for multiple comparisons, and adjusted *p*-values were presented.

Within the traditional repair group, there was one participant with VPI at the time of the MRI. In the BFP group, there were no participants diagnosed with VPI. Regarding cleft type, the traditional group contained two participants with cleft palate only, two participants with bilateral complete cleft lip and palate, and one participant with left unilateral cleft lip and palate. The BFP group contained two participants with cleft palate only, two participants with left unilateral cleft lip and palate, and one participant with right unilateral cleft lip and palate. Cleft type was not considered in this study due to the limited sample size.

Sex was not controlled for within this sample since research has shown sex effects to be nonsignificant within this age range (Perry et al., 2018). However, the normative group contained three males and two females, the traditional group contained four males and one female, and the BFP group contained all females. The normative and BFP groups were all Caucasian. The traditional repair group contained three participants who were Caucasian, one Asian, and one African American. Even though race has been shown to be significantly different between groups (Perry et al., 2018), this variable was not considered within this study because the limited sample size would not allow for statistical comparison.

Reliability. An intra-class correlation ($\alpha = .05$) was used to assess inter- and intra-rater reliability. Reliability was completed on 100% of participants using one linear and one angle measure due to angles having the lowest reliability in previously reported MR imaging studies of the VP mechanism. Inter-rater reliability was $r = .813$ for effective velar length and $r = .762$ for sagittal angle, which was calculated using separate measurements competed by two researchers with experience in 3D MRI data analyses. Intra-rater reliability was completed on the same set of angle measures 4 weeks later. Intra-rater reliability was $r = .951$ and .995, respectively, for these selected measures. Reliability of measures showed a good ($r = .75$-.90) to excellent agreement ($r = .90$+; Portney & Watkins, 2000; Table 8).

Table 8. Intraclass Correlation Results for Reliability Measures

	Inter-rater Reliability		Intra-rater Reliability	
	ICC	95% Confidence Interval	ICC	95% Confidence Interval
Sagittal Angle	.762	.291-.920	.995	.987-.998
Effective velar length	.813	.444-.937	.951	.873 - .986

ICC = intraclass correlation coefficient

Results

Participants in this study ranged from 3.00 - 7.66 years of age. The median participant age was 5.54 years. Growth was not controlled for between groups due to the low sample size and the result that participant age was not significantly different (*p* = .454) among the non-cleft (Mean = 5.97 years, Median = 5.89 years), traditional repair (Mean = 5.71 years, Median = 5.54 years), and BFP (Mean = 4.75 years, Median = 3.99 years) groups. With respect to aim II, three cases (one in each group) were excluded test-by-test for missing data. For these cases, the MRI scan quality was not high enough on these participants to distinguish the fat and muscle tissue types. All results are listed in Table 9.

Table 9. Results of Kruskal-Wallis H-test and pairwise comparisons (if applicable) are shown in the table below. Significance values have been adjusted for multiple tests. * $p < .05$

Variable (units)	Medians	H-test		Pairwise		
		χ^2	Sig.	Mean Ranks		Adj. Sig.
Effective Velar Length (mm)	BFP: 17.37	8.060	.018*	BFP: 12.20	Norm: 7.60	.312
	Cleft: 9.66			Cleft: 4.20	BFP: 12.20	.014*
	Norm: 11.83			Norm: 7.60	Cleft: 4.20	.688
Velar Thickness (mm)	BFP: 8.86	8.960	.011*	BFP: 9.60	Norm: 11.20	1.00
	Cleft: 6.70			Cleft: 3.20	BFP: 9.60	.071
	Norm: 9.13			Norm: 11.20	Cleft: 3.20	.014*
Sagittal Angle (°)	BFP: 55.0	.860	.651			
	Cleft: 57.0					
	Norm: 61.5					
Fat: Midline (%)	BFP: 18.80	10.455	.005*	BFP: 10.50	Norm: 4.50	.015*
	Cleft: 0			Cleft: 4.50	BFP: 10.50	.015*
	Norm: 0			Norm: 4.50	Cleft: 4.50	1.000
Fat: Left Paramedian (%)	BFP: 7.03	7.157	.028*	BFP: 9.50	Norm: 5.00	.062
	Cleft: 0			Cleft: 5.00	BFP: 9.50	.062
	Norm: 0			Norm: 5.00	Cleft: 5.00	1.000
Fat: Right Paramedian (%)	BFP: 14.27	10.455	.005*	BFP: 10.50	Norm: 4.50	.015*
	Cleft: 0			Cleft: 4.50	BFP: 10.50	.015*
	Norm: 0			Norm: 4.50	Cleft: 4.50	1.00
Muscle: Midline (%)	BFP: 17.01	1.077	.584			
	Cleft: 17.20					
	Norm: 14.27					
Muscle: Left Paramedian (%)	BFP: 5.53	4.269	.118			
	Cleft: 8.98					
	Norm: 13.07					
Muscle: Right Paramedian (%)	BFP: 11.12	.269	.874			
	Cleft: 10.06					
	Norm: 11.47					
Velar Stretch (mm)	BFP: 5.64	.500	.779			
	Cleft: 6.22					
	Norm: 7.40					

AIM I: To define anatomic velopharyngeal changes related to the use of a pedicled BFP graft at the time of primary palatoplasty

Velar thickness. Median values were significantly different across the three participant groups for velar thickness at midline ($\chi^2(2) = 8.960$, $p = .011$). Median velar thickness values increased from cleft without BFP (6.70 mm), to cleft with BFP repair (8.86 mm), to non-cleft (9.13 mm) groups. Pairwise comparisons were performed. Post hoc analysis revealed a statistically significant difference in velar thickness between the non-cleft (mean rank = 11.20) and cleft without BFP (mean rank = 3.20; $p = .014$) groups but not between any other group combination.

Effective velar length. Median values were significantly different among groups for effective velar length ($\chi^2(2) = 8.060$, $p = .018$). Median effective velar length values increased from cleft without BPF (9.66 mm), to non-cleft (11.83 mm), to cleft with BFP (17.37 mm) groups. Post hoc analysis revealed a statistically significant difference in effective velar length between the cleft without BFP (mean rank = 4.20) and cleft with BFP (mean rank = 12.20; $p = .014$) groups but not between any other group combination.

Sagittal angle. Median sagittal angle measure values increased from cleft with BFP (55.0°) to cleft without BFP (57.0°) to non-cleft (61.5°) groups, but these differences were not statistically significant among groups ($\chi^2(2) = .860$, $p = .651$).

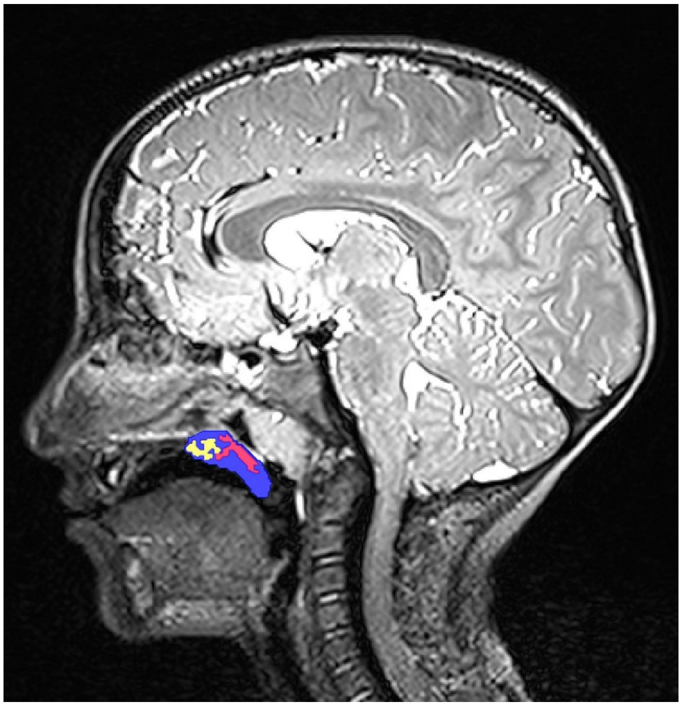
Aim II: To define tissue type within the velum related to the use of a pedicled BFP graft at the time of primary palatoplasty

Fat percentage. The three tissue types (fat, muscle, and other) are depicted in Figure 12, and cross-sectional areas are depicted in Figure 13. Median values were significantly different among the three participant groups for percentage of fat at midline ($\chi^2(2) = 10.455$, $p = .005$), left paramedian ($\chi^2(2) = 7.157$, $p = .028$), and right paramedian ($\chi^2(2) = 10.455$, $p = .005$). There were median fat percentages of 18.80%, 7.03%, and 14.27% in the midline, left paramedian, and right paramedian locations, respectively, in those with cleft palate that had undergone a repair with BFP placement; however, there was no fat within the palate for the non-cleft participants or those with cleft palate that had undergone a traditional repair. Post hoc analysis revealed statistically significant differences in fat percentage at midline and right paramedian locations between the non-cleft (mean rank = 4.50) and cleft with BFP (mean rank = 10.50; $p = .015$) and between cleft without BFP (mean rank = 4.50) and cleft with BFP (mean rank = 10.50; $p = .015$) groups.

Muscle percentage. Median values were not significantly different among the three participant groups for percentage of muscle at midline ($\chi^2(2) = 1.077$, $p = .584$), left paramedian ($\chi^2(2) = 4.269$, $p = .118$), and right paramedian ($\chi^2(2) = .269$, $p = .874$). At midline, the median muscle percentages increased from non-cleft (14.27%), to cleft with BFP (17.01%), to cleft without BFP (17.20%). At the left paramedian, the muscle percentages increased from cleft with BFP (5.53%), to cleft without BFP (8.98%), to non-cleft (13.07%) groups. At the right paramedian, the muscle percentages increased from cleft without BFP (10.06%), to cleft with BFP (11.12%), to non-cleft (11.47%) groups.

Figure 12. Tissue types are outlined in the midsagittal view as follows: red = muscle, yellow = fat, blue = other

Figure 13. Tissue segmentation is generated and overlaid on the midsagittal image plane as follows: red = muscle, yellow = fat, blue = other



Aim III: To determine if the use of a pedicled BFP graft at the time of primary palatoplasty results in greater velar stretch for speech compared to children with cleft palate without BFP

Velar stretch. Velar stretch medians increased from cleft with BFP (5.64 mm) to cleft without BFP (6.22 mm) to non-cleft (7.40 mm) groups. These differences were not statistically significant across groups ($\chi^2(2) = .500$, $p = .779$).

Discussion

Various surgical techniques are currently used during primary palatoplasty. Similarly, surgical techniques differ among surgical centers and surgeons themselves (Agrawal, 2009). The current literature suggests that positive outcomes are only apparent approximately 70-80% of the time regardless of the type of procedure used (Marsh, Grames, & Holtman, 1989; Moore, Lawrence, Ptak, & Trier, 1988; Musgrave & Bremner, 1960; Phua & de Chalain, 2008; Sullivan, Marrinan, LaBrie, Rogers, & Mulliken, 2009). Past research has sought to determine which anatomical markers are predictive of VPD. Reduced palate length, increased pharyngeal depth, reduced velar stretch, decreased palatal muscle volume, anterior placement of levator muscle fibers, and lack of midline muscle mass have all been raised as potential predictors of VPD (D'Antonio et al., 2000; Ha et al., 2007; Inouye et al., 2016; Kotlarek et al., 2017; Pruzansky & Mason, 1969; Randall et al., 2000; Tian et al., 2010a,b; Zhang et al., 2010). The BFP graft (or flap) has been a well-documented technique in primary palatoplasty (Kim, 2001; Levi et al., 2009; Pappachan & Vasant, 2008; Pinto & Debnath, 2007; Yamaguchi et al., 2016; Zhang, et al. 2010). These clinical case studies have suggested this technique creates a more favorable system for velopharyngeal closure by increasing velar length, maintaining posterior levator muscle position, and adding tissue to an otherwise deficient area (Levi et al., 2009; Pappachan & Vasant, 2008; Zhang, et al. 2010)

Data from this study systematically evaluated whether BFP graft placement at the palatine aponeurosis during the time of primary palatoplasty creates more favorable velopharyngeal dimensions for adequate closure. Using MRI, participants who had received a BFP graft were compared to both non-cleft participants as well as participants who had a primary palatoplasty using a traditional surgical technique (without BFP). Quantitative details regarding the anatomic and physiologic impact of the use of BFP during primary palatoplasty were obtained.

Anatomical Changes (Aim I)

Aim I was designed to assess anatomical changes in the velum post-operatively within the BFP group and compare these changes to both a normative group as well as a group with repaired cleft palate having received a traditional repair (without BFP). Significant differences were observed for effective velar length and velar thickness. Nonsignificant differences were observed for sagittal angle.

Velar thickness was greatest in the normative group. The median velar thickness for the normative group was only 0.27 mm greater than that of the BFP group, a difference that was not statistically significant in post hoc analysis. However, the difference between the traditional repair group and the normative group was statistically significant (2.43 mm). Based on this study, the BFP graft was able to overcome the midline deficiency characteristic common to individuals with repaired cleft palate with the addition of adipose tissue. The velar thickness measurement was taken at the velar knee, which is the most muscular part of the velum due to the insertion of the levator muscle in that region. Interestingly, the fat from the BFP graft itself did not account for this increase in thickness, as the fat did not extent posteriorly enough to the level of the velar knee where velar thickness is acquired from. This finding does, however, indicate that the BFP graft was able to maintain the posterior positioning of the levator muscle and associated muscle thickness at the velar knee.

Effective velar length was far greater in the BFP group than either of the two comparison groups. Post hoc analysis revealed a significant difference was observed between the traditional repair and BFP groups only. This finding offers quantitative support that the BFP graft is maintained to some degree within the palate at least five years after repair and acts to prevent the levator muscle fibers from moving anteriorly while increasing the effective velar length. Tian and colleagues (2010a) found effective velar length was found to be different between three groups of children, including those with repaired cleft palate with and without VPI. Effective velar length may be a significant surgical predictor of future need for secondary surgical intervention. Since the BFP graft creates an increased effective velar length, it may be likely that surgery using the BFP graft may reduce the need for secondary surgical intervention for VPI.

Individuals with cleft palate have an absent posterior nasal spine, and depending on the anatomy of the cleft itself, the posterior border of the hard palate is likely also displaced anteriorly even after palate repair. Because this point is moved anteriorly, the anterior measurement point for velar length and effective velar length are positioned anteriorly in participants with cleft palate. Radiographic assessments have traditionally used the pterygomaxillary fissure rather than the posterior hard palate as a measurement point to overcome this difference. However, this poses two issues when assessing soft tissue structures using MRI: 1) the pterygomaxillary fissure is not easily visualized via MRI as it is a bony structure, and 2) the velum has tissue properties different than that of the bony hard palate and therefore need to be considered separately. The velum of an individual with a repaired cleft palate does not have typical boundaries, and therefore, needs to be considered separate from the normative group. Due to this difference, the effective velar length would be longer in an individual with repaired cleft palate if the angle of levator insertion into the palate (sagittal angle) was restored post-operatively. The data in the present study supports this idea because the effective velar length is longer in the BFP group than in the normative group.

The sagittal angle, or angle with which the levator muscle inserts into the body of the velum as referenced to the spinal column was not significant between groups in this study. All group medians were within 6.5 degrees of each other. This went against the hypothesis that predicted the sagittal angle would be significantly different between the traditional repair and BFP groups and more similar between the BFP and non-cleft groups. This finding was likely impacted by head positioning of participants within the MRI. Two of the participants in the BFP group were looking down toward their feet in the headcoil while the MRI was running. This reference greatly changed the positioning of the velum in reference to the 3rd and 4th vertebrae, which was the reference line utilized in this study to create the sagittal angle. Measuring the sagittal angle from a vertebral reference that was more caudally oriented would likely yield a more accurate measure.

Tissue Changes (Aim II)

Aim II was designed to assess tissue changes in the velum post-operatively within the BFP group and compare these changes to both a normative group as well as a group with repaired cleft palate having received a traditional repair (without BFP). Significant differences were observed for percentage of fat at midline, left paramedian, and right paramedian locations. Nonsignificant differences were observed for all locations with respect to muscular percentage.

The percentage of fat within the velum was significantly different between groups at all cross-sectional locations within the velum. This finding was congruent with our hypothesis and previous literature, indicating the fat tissue was maintained within the palate five years post-operatively. No noticeable fat was present within the velum for participants in the traditional repair and normative groups, which was expected. All participants in the BFP group had noticeable fat tissue posterior to the bony hard palate, which was also expected.

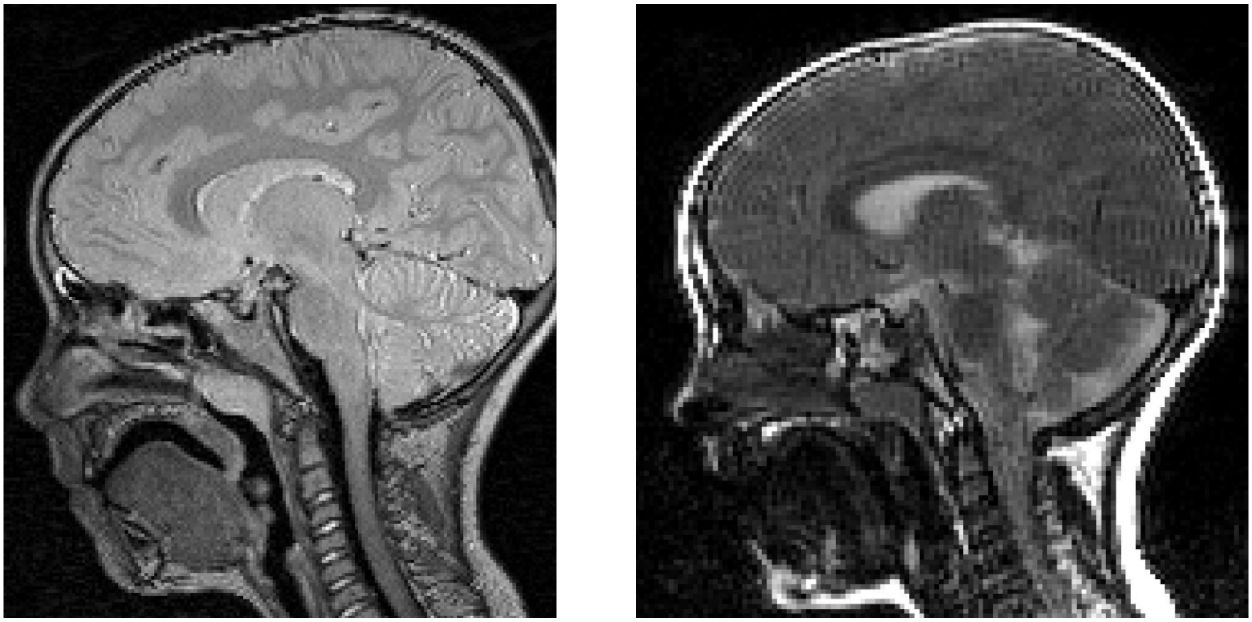
Regarding fat percentage, post hoc analyses were significant between the BFP and traditional repair groups as well as BFP and non-cleft groups for the midline and the right paramedian cross-sectional areas. The aforementioned differences between groups were approaching significance for the left paramedian location. The median left fat percentage was potentially impacted by one participant in the BFP group who did not have any fat tissue present in the left side of the velum. This participant received a unilateral BFP graft from the right side, so it is possible that the BFP graft did not reach the contralateral side during surgery. However, it is unknown whether the BFP retracted back to the right side in this participant with healing or if it was ever present in the left side. Two other participants received unilateral BFP grafts from the right side; both of those participants possessed fat across all three locations in the palate, as did the one participant who received a unilateral BFP graft form the left side. This is of clinical importance when considering whether to utilize a unilateral or bilateral BFP graft approach.

The muscular percentage of the velum, as assessed by three anterior-posterior cross-sectional areas, was not significant between the three participant groups. Median values of muscular percentage ranged from 5.53% to 17.20% across all groups and positions. The normative group had the greatest percentage of muscle at both left and right paramedian cross-sections. At midline, the traditional repair and BFP groups had the greatest median percentage of muscle at 17.20% and 17.01%, respectively. This increase in muscle mass at midline within both cleft groups was not anticipated. However, it is plausible that the type of surgical soft palate closure impacted these results. During primary palatoplasty, the levator muscle bundles are commonly dissected form the hard palate and overlapped to a certain degree depending on the specific surgical technique. It is unknown what degree of overlap was obtained during surgery for the participants in this study, and this should be considered as a variable in future investigations of tissue type within repaired cleft palate.

Physiological Changes (Aim III)

Aim III was designed to assess physiological changes in the velum post-operatively within the BFP group and compare these changes to both a normative group as well as a group with repaired cleft palate having received a traditional repair (without BFP). Figure 14 shows the velum at rest and elevated during sustained speech, which were used to calculate velar stretch. Nonsignificant differences were observed for measures of velar stretch. All group medians were within 1.76 mm of each other. The greatest velar stretch was observed in the non-cleft group. Although this finding was not aligned with our hypothesis, there is a lot of room for variability within this measure.

Figure 14. Midsagittal image of the velum at rest (left) and during sustained phonation (right).



Velar stretch is not a measure of absolute capacity. In other words, the ability of the velum to stretch to achieve velopharyngeal closure is not being assessed but rather the *necessity* for the velum to stretch. The velum only stretches as far as it must until it reaches closure against the posterior pharyngeal wall, or more likely an adenoid pad in children (J. Riski, personal communication, 2018). Qualitatively, the children in this study had varying degrees of adenoid tissue, but adenoid depth was not measured as part of this study. Adenoid depth in relation to velar stretch in the normative population should be well-defined before future comparisons to repaired cleft anatomy.

Limitations

This study has a number of limitations which impacts conclusions drawn from the study and generalization to cleft population in general. First, the study consisted of a very small sample. Participants eligible for this type of study are of low numbers and studies with small sample sizes must be completed to advance this work. The PI recognizes and accepts this limitation given the early stage of this work.

A second limitation of study is related to the variations in surgical technique that were not considered in the present study. Although participants with the BFP graft were recruited from a single surgeon's clinical population, the soft palate closure technique varied between participants. In addition, the BFP procedure was not identical between participants, as some participants had bilateral BFPs placed during the primary palatoplasty while others had only a unilateral BFP pulled into the palate. An increased sample size is also needed to control for theses variables.

A third limitation is related to the imaging techniques utilized. Categorization of tissue type by T2-weighted images should be interpreted with caution. Although the volumetric, anatomical MRI sequences utilized in this study are high-resolution, gross anatomy classification cannot replace traditional histological assessment or more advanced imaging techniques, such as diffusion tensor imaging. Yet the approaches utilized in this study are a novel application of previously published research on tissue composition (Bae et al., 2016) to the study of surgical impact to the velopharyngeal mechanism and are necessary to advance the science in this area.

Future Directions

Future research is needed to identify patient-specific factors that may predict the best candidates for different surgical techniques. All but one of the participants in the present study presented with a competent velopharyngeal mechanism, meaning velopharyngeal closure was achieved during speech despite the type of surgical repair. Additional research regarding which patients benefit most from specific surgical techniques is required for clinical relevance. In addition, race, growth, and surgical technique for soft palate closure were not controlled for in the present study. An increased sample size is required to control for such variables, improve generalization of findings, and have better acceptability of the statistical methods utilized. Since the BFP appears to maintain its tissue properties post-surgically, computational modeling regarding the impact of fat tissue at the posterior hard palate on velar closure force is warranted. Application of advanced imaging modalities, such as diffusion tensor imaging, may expand upon the tissue-related findings in the present study and provide more detailed histological data.

Conclusion

Data from this study confirmed that BFP graft placement during the time of primary palatoplasty alters individual anatomy up to five years postoperatively. Significant differences across groups were noted for effective velar length, velar thickness, and percentage of fat within the body of the velum. Participants treated with the BFP graft had the greatest effective velar length when compared the normative group as well as those with a traditionally-repaired cleft palate. Velar thickness was greatest in the normative group and nearly normalized within the BFP group. MRI confirmed that encapsulated fat was present at the midline as well as to the left and right paramedian in the BFP group. Further research is needed to assess the impact of soft palate closure technique within the BFP group and determine patient-specific factors that may predict the best candidates for this surgical approach.

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CHAPTER 6

GENERAL CONCLUSION

Although children with cleft palate typically undergo primary palatoplasty prior to 12 months of age, about one-third of these children require secondary surgical intervention to eliminate hypernasal speech due to velopharyngeal dysfunction (VPD). The literature is still inconclusive regarding what variables predispose an individual with repaired cleft palate to develop VPD. This research utilized magnetic resonance imaging (MRI) to assess changes to the velopharyngeal port and levator veli palatini (levator) muscle caused by surgical intervention to the palate. A series of investigations were completed to assess post-surgical anatomical and physiological changes to the velopharynx in participants with repaired cleft palate.

Study I focused on differences in the form of the levator veli palatini (levator) muscle in adults with cleft and non-cleft anatomy. Results indicated that differences between groups were present for measures of total muscle volume, circumference at the levator muscle origin and insertion, anterior-posterior diameter at the origin and midline, and superior-inferior diameter at the point of insertion into the velum and midline. These findings provided insight into the impact surgery has on the levator muscle in adults who are several decades past initial palate repair.

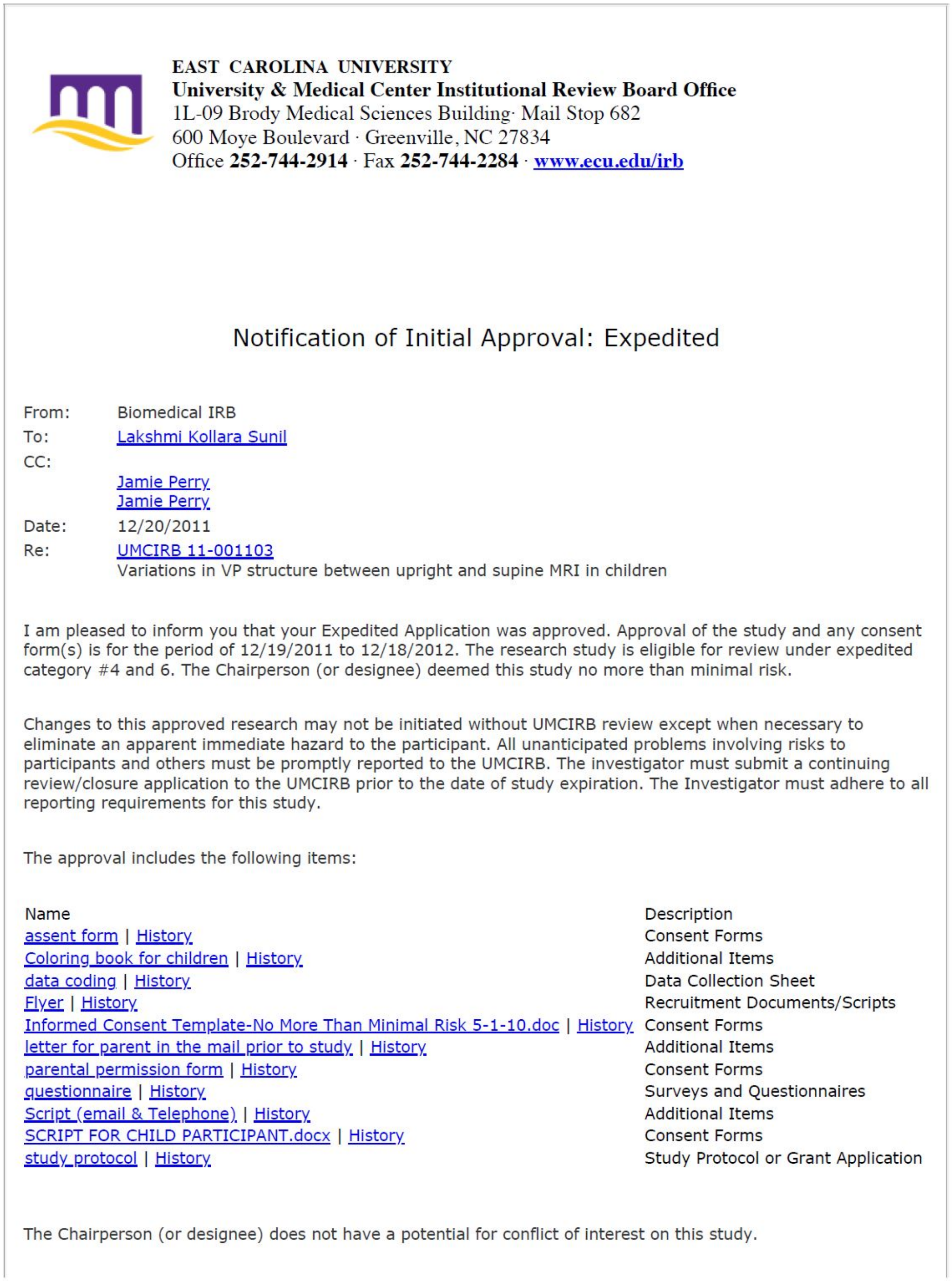
Study II determined if there was any asymmetry or positional differences within the velopharynx or levator muscle between children without a cleft palate, those with cleft palate with complete velopharyngeal closure, and those with cleft palate and VPD. Median values were significantly different between groups for variables of sagittal angle, effective velopharyngeal ratio, extravelar muscle length, and levator muscle thickness at midline. Thickness between the left and right levator muscle bundles at the point if insertion into the velum was also significantly different among groups. Findings indicated that velopharyngeal and levator variables are different regardless of velopharyngeal status, but the most asymmetry is seen within the population with VPD.

Study III compared velopharyngeal anatomy and physiology among children with cleft palate who have undergone primary palatoplasty with buccal fat pad (BFP) graft placement to those who have undergone more traditional surgical methods as well as a normative control group. Variables of velar thickness, effective velar length. and percentage of fat within the velum were significantly different across groups. This study confirms participants who underwent primary palatoplasty with BFP graft placement showed an increase in adipose tissue within the velum and increased effective velar length up to five years post-operatively. This may create more favorable dimensions for velopharyngeal closure.

This study provides preliminary data for future investigations regarding the post-operative anatomy and physiology of individuals with cleft palate using larger numbers of participants and controlling for surgical repair technique. Further research in this area may identify patient-specific variables that result in a successful primary palatoplasty and reduce the need for secondary surgical intervention. Advancements in imaging technology and their continued application to evaluating the velopharyngeal mechanism will improve clinical decision-making and surgical outcomes for children born with cleft palate.

APPENDICES

APPENDIX A. INITIAL IRB NOTIFICATION OF APPROVAL



EAST CAROLINA UNIVERSITY
University & Medical Center Institutional Review Board Office
1L-09 Brody Medical Sciences Building· Mail Stop 682
600 Moye Boulevard · Greenville, NC 27834
Office **252-744-2914** · Fax **252-744-2284** · **www.ecu.edu/irb**

Notification of Initial Approval: Expedited

From: Biomedical IRB
To: Lakshmi Kollara Sunil
CC:
Jamie Perry
Jamie Perry
Date: 12/20/2011
Re: UMCIRB 11-001103
Variations in VP structure between upright and supine MRI in children

I am pleased to inform you that your Expedited Application was approved. Approval of the study and any consent form(s) is for the period of 12/19/2011 to 12/18/2012. The research study is eligible for review under expedited category #4 and 6. The Chairperson (or designee) deemed this study no more than minimal risk.

Changes to this approved research may not be initiated without UMCIRB review except when necessary to eliminate an apparent immediate hazard to the participant. All unanticipated problems involving risks to participants and others must be promptly reported to the UMCIRB. The investigator must submit a continuing review/closure application to the UMCIRB prior to the date of study expiration. The Investigator must adhere to all reporting requirements for this study.

The approval includes the following items:

Name	Description
assent form | History	Consent Forms
Coloring book for children | History	Additional Items
data coding | History	Data Collection Sheet
Flyer | History	Recruitment Documents/Scripts
Informed Consent Template-No More Than Minimal Risk 5-1-10.doc | History	Consent Forms
letter for parent in the mail prior to study | History	Additional Items
parental permission form | History	Consent Forms
questionnaire | History	Surveys and Questionnaires
Script (email & Telephone) | History	Additional Items
SCRIPT FOR CHILD PARTICIPANT.docx | History	Consent Forms
study protocol | History	Study Protocol or Grant Application

The Chairperson (or designee) does not have a potential for conflict of interest on this study.

IRB00000705 East Carolina U IRB #1 (Biomedical) IORG0000418
IRB00003781 East Carolina U IRB #2 (Behavioral/SS) IORG0000418 IRB00004973
East Carolina U IRB #4 (Behavioral/SS Summer) IORG0000418

APPENDIX B. IRB AMENDMENT APPROVAL LETTER

EAST CAROLINA UNIVERSITY
University & Medical Center Institutional Review Board Office
4N-70 Brody Medical Sciences Building· Mail Stop 682
600 Moye Boulevard · Greenville, NC 27834
Office **252-744-2914** · Fax **252-744-2284** · www.ecu.edu/irb

Notification of Amendment Approval

From: Biomedical IRB
To: Jamie Perry
CC:
Jamie Perry
Jamie Perry
Date: 2/6/2017
Re: Ame13_UMCIRB 11-001103
UMCIRB 11-001103
Variations in VP structure between upright and supine MRI in children and adults

Your Amendment has been reviewed and approved using expedited review for the period of 2/3/2017 to 12/16/2017. It was the determination of the UMCIRB Chairperson (or designee) that this revision does not impact the overall risk/benefit ratio of the study and is appropriate for the population and procedures proposed.

Please note that any further changes to this approved research may not be initiated without UMCIRB review except when necessary to eliminate an apparent immediate hazard to the participant. All unanticipated problems involving risks to participants and others must be promptly reported to the UMCIRB. A continuing or final review must be submitted to the UMCIRB prior to the date of study expiration.The investigator must adhere to all reporting requirements for this study.

Approved consent documents with the IRB approval date stamped on the document should be used to consent participants (consent documents with the IRB approval date stamp are found under the Documents tab in the study workspace).

The approval includes the following items:

Document	Description
Assent form- amendment 11 (clean copy).docx(0.01)	Consent Forms
Assent form- amendment 11 (tracked changes).docx(0.01)	Consent Forms
flyer-amendment 6 (clean copy).docx(0.01)	Recruitment Documents/Scripts
flyer-amendment 6 (tracked changes).docx(0.01)	Recruitment Documents/Scripts
questionnaire- amendment 7 (clean copy).docx(0.01)	Surveys and Questionnaires
questionnaire- amendment 7 (tracked changes).docx(0.01)	Surveys and Questionnaires

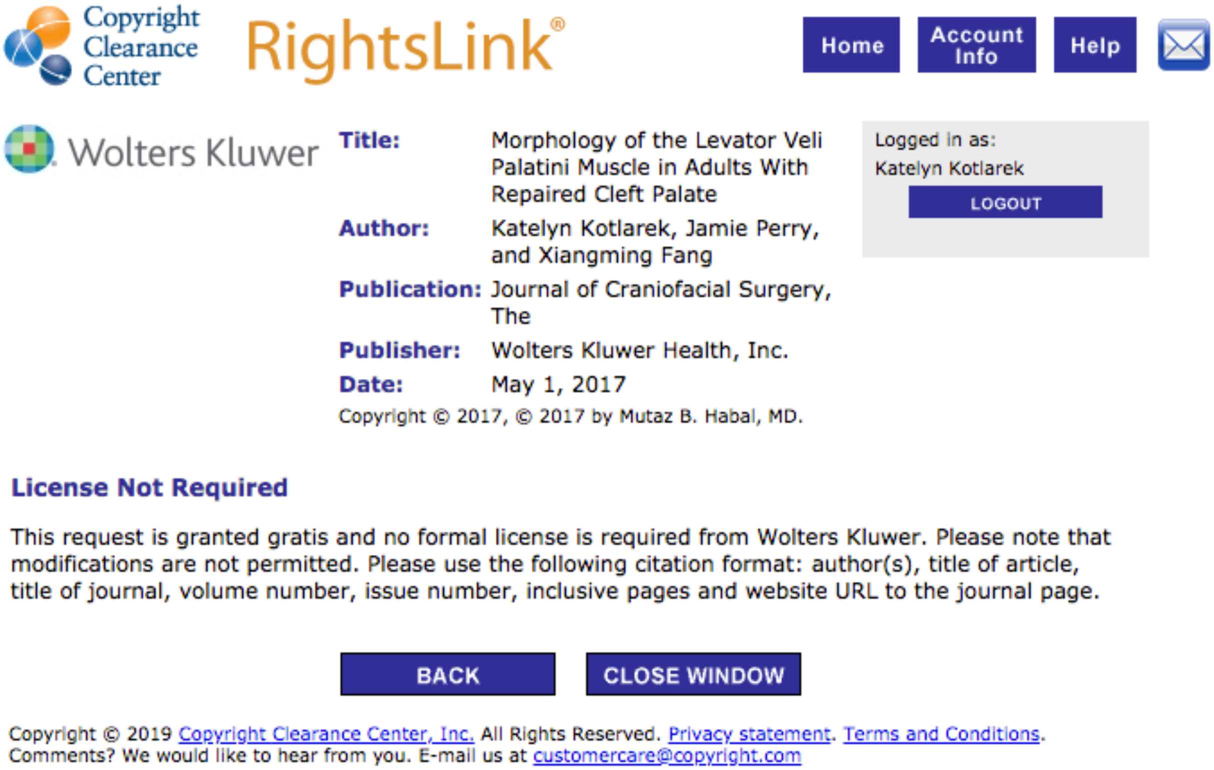
Sub Investigators Added: Kotlarek & Mason

The Chairperson (or designee) does not have a potential for conflict of interest on this study.

IRB00000705 East Carolina U IRB #1 (Biomedical) IORG0000418
IRB00003781 East Carolina U IRB #2 (Behavioral/SS) IORG0000418

APPENDIX C: RIGHT TO REUSE PUBLISHED MANUSCRIPTS IN DISSERTATION

Study I. Journal of Craniofacial Surgery



Title: Morphology of the Levator Veli Palatini Muscle in Adults With Repaired Cleft Palate

Author: Katelyn Kotlarek, Jamie Perry, and Xiangming Fang

Publication: Journal of Craniofacial Surgery, The

Publisher: Wolters Kluwer Health, Inc.

Date: May 1, 2017

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Logged in as:
Katelyn Kotlarek

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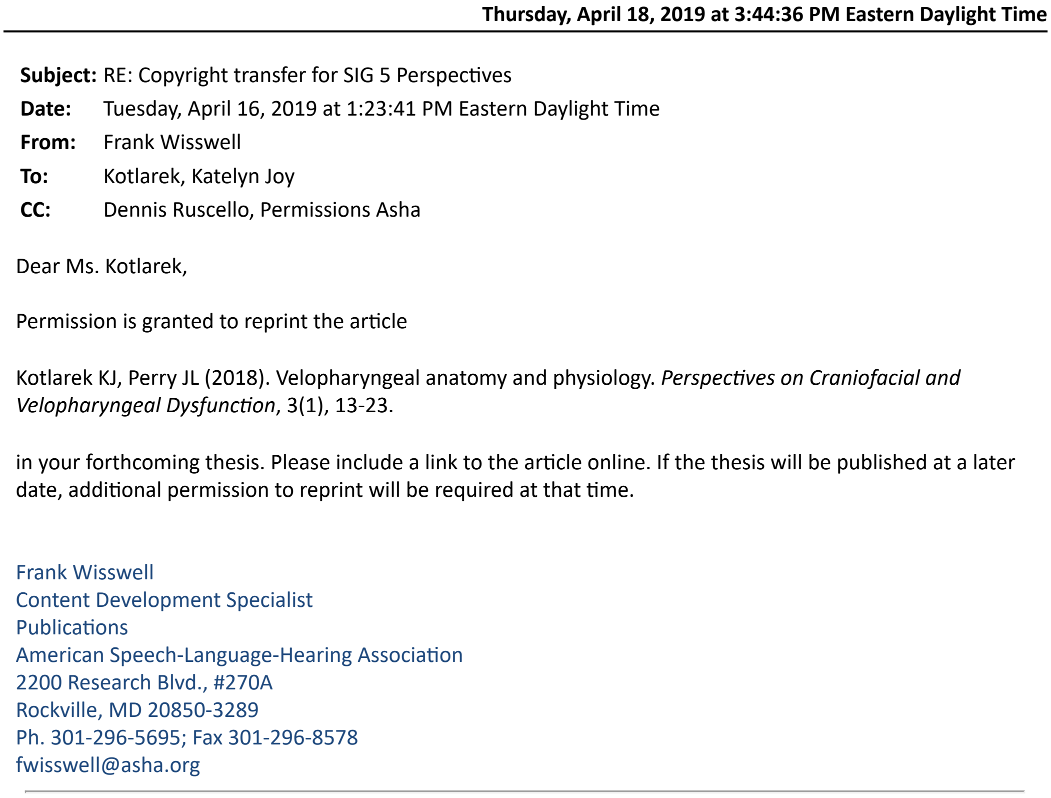
Comments? We would like to hear from you. E-mail us at customercare@copyright.com

Study II. Perspectives on Craniofacial and Velopharyngeal Dysfunction



Thursday, April 18, 2019 at 3:44:36 PM Eastern Daylight Time

Subject: RE: Copyright transfer for SIG 5 Perspectives
Date: Tuesday, April 16, 2019 at 1:23:41 PM Eastern Daylight Time
From: Frank Wisswell
To: Kotlarek, Katelyn Joy
CC: Dennis Ruscello, Permissions Asha

Dear Ms. Kotlarek,

Permission is granted to reprint the article

Kotlarek KJ, Perry JL (2018). Velopharyngeal anatomy and physiology. *Perspectives on Craniofacial and Velopharyngeal Dysfunction*, 3(1), 13-23.

in your forthcoming thesis. Please include a link to the article online. If the thesis will be published at a later date, additional permission to reprint will be required at that time.

Frank Wisswell
Content Development Specialist
Publications
American Speech-Language-Hearing Association
2200 Research Blvd., #270A
Rockville, MD 20850-3289
Ph. 301-296-5695; Fax 301-296-8578
fwisswell@asha.org

URL: *https://pubs.asha.org/doi/full/10.1044/persp3.SIG5.13*