Reviewing and Refining Surgical Interventions for Glottic Insufficiency

By

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ABSTRACT

Glottic insufficiency is the primary anatomic etiology of dysphonia and a central abnormality of disorders such as vocal fold paralysis, presbylaryngis, and vocal fold scar. Treatment is primarily surgical and directed towards placing the affected fold in a midline position conducive to glottic closure and vocal fold vibration. Two open procedures offering permanent medialization include type I thyroplasty and arytenoid adduction. Thyroplasty uses an implant to medialize the affected vocal fold while arytenoid adduction uses a suture technique to accomplish the same goal. Though valuable and capable of providing a good outcome, both procedures are technically challenging and highly invasive. This series of seven studies used the excised larynx bench apparatus to perform a systematic, multiparametric assessment of current treatments and evaluate new devices which could simplify the procedures. Specifically, an adjustable silicone balloon implant which can be inserted via a minimally invasive minithyrotomy and a suture-wire complex which can be used to perform arytenoid adduction from a less invasive anterior approach were investigated. Experiments were performed using excised canine larynges and treatments were compared to both simulated unilateral vocal fold paralysis as well as normal conditions. Additionally, a range of aerodynamic, acoustic, and videokymographic parameters were employed and their ability to describe changes in phonation due to vocal fold medialization individually and collectively was determined. Vocal efficiency and perturbation parameters were demonstrated to be particularly effective at describing changes in laryngeal function as the arytenoid is rotated during arytenoid adduction. The wedge-shaped adjustable balloon implant provided effective medialization, closing the glottic gap and restoring normal vocal fold vibration. The suture-wire complex was effective for performing arytenoid adduction from an anterior aspect, thus eliminating the most challenging aspect of the procedure.
while not sacrificing outcome quality as judged by comparison to the traditional procedure. Further studies evaluating host response and long-term stability of these devices in living animals and human subjects are warranted.

Adviser signature: 

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CHAPTER 1
Introduction

A. INTRODUCTION TO AND MOTIVATION FOR STUDY

The larynx plays a crucial role in numerous physiological processes, including breathing, swallowing, speaking, coughing, vomiting, laughing, and crying. Importantly, these actions frequently overlap and all must occur in the context of respiration. Though maintenance of airway patency during breathing and closure during swallowing are the primary vital functions of the larynx, the non-essential function of voice production captivates our interest and drives much of the research on laryngeal physiology. Voice is a critical component of personal identity and complex speech production represents a key evolutionary achievement unique to humans. Normal functioning of the larynx is dependent upon symmetric vocal fold approximation, accomplished via intricate and coordinated contractions of its intrinsic muscles.

Glottic insufficiency, or the inability to achieve vocal fold approximation, is the primary etiology of dysphonia and can adversely affect all processes in which the larynx plays a part. It is the key underlying feature in numerous disorders such as vocal fold paralysis, vocal fold scar, intubation injury, and presbylaryngis, and can also occur in many neurological diseases. Current commonly used treatments for glottic insufficiency include injection laryngoplasty, medialization thyroplasty, and arytenoid adduction. Injection medializes an affected fold by increasing its volume; limitations include absorption, limited duration, and inability to revise a suboptimal procedure. Medialization thyroplasty and arytenoid adduction have the potential to
produce dramatic improvements in laryngeal function when performed correctly; however, technical challenges and a high degree of invasiveness have prevented their widespread application. Accordingly, significant research proposing new methods of treating this disorder has been conducted. Despite the vast amount of papers touting the next advance in vocal fold medialization, most procedures are quite invasive and voice restoration remains challenging.

I describe a series of studies which evaluates current surgical interventions and proposes alternatives to address treatment limitations. All experiments were conducted using the excised larynx bench apparatus with a variety of outcome measures, including aerodynamic, acoustic, and videokymographic parameters. Studies include evaluations of current treatments and implants, use of real-time quantitative voice parameters to optimize arytenoid adduction, machine learning-based classification of glottic insufficiency and tension asymmetry, and presentation of new devices capable of facilitating less invasive thyroplasty and arytenoid adduction. Background information on normal and disordered laryngeal physiology is presented with an emphasis on glottic insufficiency and specifically, vocal fold paralysis. The ultimate goal of this research is to develop a simple method of performing minimally invasive permanent vocal fold medialization.

B. GENERAL STRUCTURE OF AND INNERVATION TO THE LARYNX

B.1 Structural support

Structural support for the larynx is provided by the hyoid bone and six cartilages, three of which are paired (Tucker 1993). The largest cartilage is the thyroid, the angle of which is approximately 90 degrees in males and 120 degrees in females, accounting for the difference in
external prominence. It is connected to the hyoid bone via the thyrohyoid membrane and to the epiglottis via the thyroepiglottic ligament. The epiglottis is similar in shape to the tongue of a shoe and serves to cover the entrance to the airway during swallowing; it can also serve as a resonance chamber during phonation (Titze 2000). The ring-shaped cricoid cartilage marks the inferior boundary of the larynx and is attached to the trachea via the cricotracheal ligament. The cricoid is asymmetric, with a longer vertical extent posteriorly. The posteriorly positioned cricoarytenoid facets provide the articulatory surfaces for the paired arytenoid cartilages. The shape of the cricoarytenoid joint allows for sliding, rocking, and twisting (Hunter 2005). Key aspects of the arytenoid cartilages include the muscular and vocal processes. The muscular process serves as the point of attachment for all intrinsic muscles except the cricothyroid muscles while the vocal process serves as the point of attachment for the vocal ligament. Superior to each arytenoid cartilage is the corniculate cartilage. The cuneiform cartilages are positioned anterosuperiorly to the corniculates and lie within the aryepiglottic fold.

Arytenoid range of motion was described by Hunter and Titze (Hunter 2005). Movement can be described using a three-dimensional coordinate system, where anterior-posterior movement is in the Y axis, medial-lateral movement is in the X axis, and superior-inferior movement is in the Z axis. Using the medial edge of the vocal process as a landmark, the arytenoid moves 2.2 mm with contraction of the posterior cricoarytenoid, predominately laterally, 2.2 mm with contraction of the lateral cricoarytenoid, predominately inferiorly and medially, 1.3 mm with contraction of the interarytenoid, predominately superiorly, 1.4 mm with contraction of the thyromuscularis, predominately inferiorly, and 0.4 mm with contraction of the thyrovocalis, with no predominate axis of movement (Hunter 2005).
B.2 Musculature and proximal innervation

Intrinsic muscles of the larynx controlled by the recurrent laryngeal nerve (RLN) include the thyroarytenoid, lateral cricoarytenoid, posterior cricoarytenoid, and interarytenoid muscles. Peripheral innervation to the interarytenoid muscles is bilateral, while innervation to the others is unilateral. The only muscle not innervated by the RLN, the cricothyroid muscle, controls vocal fold elongation and is innervated by the superior laryngeal nerve (SLN). The lateral cricoarytenoid and thyroarytenoid are the primary adductor muscles; loss of innervation results in glottic incompetence with resultant breathy phonation and susceptibility to aspiration. The posterior cricoarytenoid is the sole abductor muscle. The most important role of the posterior cricoarytenoid muscle is in respiration, where contraction leads to vocal fold abduction which opens the airway, but it also plays a key role during voice production. Contraction allows the arytenoid to rock posteriorly, increasing the tension on the vocal ligament. If innervation to the posterior cricoarytenoid is lost, the arytenoid tends to subluxate anteromedially as there is no posteriorly directed force to counter anterior movement (Crumley 1994). Sensory innervation to the larynx is from the internal branch of the SLN above the glottis and the RLN at and below the glottis.

B.3 Vocal fold

The outermost layer of the vocal fold is stratified squamous epithelium, able to withstand the stress of vibration during voice production. Deep to the epithelium is the three-layered lamina propria. The superficial layer, or Reinke’s space, consists of scattered elastin fibers surrounded by extracellular matrix and plays a key role in vocal fold vibration (Titze 2000). The intermediate and deep layers combine to form the vocal ligament, with the intermediate layer
consisting predominately of elastin and the deep layer consisting predominately of collagen. Deep to the lamina propria is the thyroarytenoid muscle, which provides the bulk of the vocal fold (Titze 2000). Hirano’s body-cover scheme divides the vocal fold into two layers: a cover consisting of epithelium, superficial lamina propria, and intermediate lamina propria, and a body consisting of deep lamina propria and muscle (Hirano 1985).

Superior to the true vocal folds are the false vocal folds, or ventricular folds. The false vocal folds regulate pressure between the thoracic and abdominal cavities and can also contribute to normal voice production and timbre (Pressman 1941; Young 2012; Lindestad 2004). Ventricular folds also play a prominent role in Tibetan monk throat singing. According to a recent electrophysiological and anatomical study by Young et al., ventricular fold adduction appears to be due to contraction of the ventricularis muscle which is controlled by the RLN (Young 2012).

**B.4 Vascular supply**

Vascular supply to the larynx is from the superior and inferior laryngeal arteries, which are branches of the superior and inferior thyroid arteries, respectively. The superior thyroid artery arises from the external carotid artery, while the inferior thyroid artery arises from the thyrocervical trunk. Venous drainage parallels arterial supply and is via the superior and inferior laryngeal veins. These laryngeal veins arise directly from the thyroid veins, which are branches of the jugular vein (Tucker 1993).

**B.5 Higher level innervation**

The larynx plays critical roles in a variety of activities, including speaking, swallowing, coughing, laughing, and crying. Accordingly, the relationships among the neural structures
which control laryngeal activity are rather complex. Each task (i.e., phonation, respiration, swallowing) is governed by a different central pattern generator in the medulla, and relationships among these allow for coordinated laryngeal activities (for a review, see Jean 2001). The pattern generators exert control over laryngeal motor neurons but also serve as an interface between the larynx and the central systems which participate in its control (Van Daele 2009).

A detailed description of the neural pathways underlying voice production is provided by Jurgens (Jurgens 2002). Briefly, nuclei for motor neurons governing voice include the: trigeminal motor nucleus in the pons; facial nucleus, nucleus ambiguus, and hypoglossal nucleus in the medulla; and ventral horn of the spinal cord in the cervical, thoracic, and lumbar regions (Jurgens 2002). Coordination of these nuclei is accomplished via a network consisting of the ventrolateral parabrachial area, lateral pontine reticular formation, anterolateral and caudal medullary reticular formation, and nucleus retroambiguus (Jurgens 2002). Voluntary control of vocalization also requires input from the cerebral cortex, including Broca’s area, the supplementary motor area, and the pre-supplementary motor area (Jurgens 2002). Corticobulbar fibers descend from the cerebral cortex through the internal capsule to synapse in the nucleus ambiguus (Rosen 2008). The nucleus ambiguus contains the cell bodies for the vagus nerve, which gives rise to the RLN. The RLN innervates most of the intrinsic laryngeal muscles, including the thyroarytenoid. This muscle provides the bulk of the vocal fold and plays a key role during swallowing, phonation, respiration, and cough (McCulloch 1996). Its higher level innervation has been studied in depth by Van Daele and Cassell (2009) and reviewed by McCulloch et al. (2011). Using pseudorabies virus and green fluorescent protein injected into the thyroarytenoid muscles, Van Daele and Cassell determined that multiple forebrain systems
innervate the thyroarytenoid muscles. Three distinct but interconnected suprabulbar systems were particularly notable (Van Daele 2009). The first consists of the anterior cingulate, periaqueductal gray, and ventral respiratory group; these structures serve as the origin of vocalization in primates (Jurgens 2002). The second consists of the central nucleus of the amygdala, basal ganglia, thalamus, and hypothalamus; this group is required for complex branchiomotor functions such as swallowing and also for conditioned vocalization in response to aversive stimuli. These connections to the limbic system may also play a role in the control of respiratory muscles (Straus 1997) and functions of the larynx such as laughing or crying (McCulloch 2011). Third, the ventrolateral preoptic area of the hypothalamus provides neural input; this is likely required for tonic thyroarytenoid activity during sleep.

C. GLOTTIC INSUFFICIENCY

Abnormal neural input or muscular function or structure can impair normal laryngeal function. Glottic insufficiency, or inability to achieve vocal fold approximation, is the primary anatomic etiology of dysphonia (Isshiki 1998). It is a common problem encountered in otolaryngology (Mortensen 2009) that has a variety of causes, including vocal fold paralysis, vocal fold scar, intubation injury, and presbylaryngis. Importantly, impaired vocal fold approximation adversely affects voice production, predisposes patients to aspiration, and has significant impacts on quality of life (Havas 1999; Spector 2001).

C.1 Aging and presbylaryngis

Presbyphonia, or aging voice, is a condition caused by age-related changes in anatomy and physiology. Adverse changes in phonation can be due to paresis, vocal fold bowing, or
systemic neurological changes such as tremor (Ford 2004). It is a very common problem, with a prevalence of approximately 20-29% (Turley 2009; Roy 2007). Importantly, 13% report moderate to profound effects on quality of life (Golub 2006) and elderly patients cognizant of voice deterioration tend to avoid social situations (Verdonck-de Leeuw 2004).

Specific changes in laryngeal anatomy associated with aging were highlighted in a cadaveric study by Hirano et al., who evaluated sixty-four larynges obtained from persons who were 70-104 years old at time of death (Hirano 1989). Compared to specimens obtained from younger persons, these larynges exhibited shortening of the membranous vocal fold, thickening of the mucosa, increased edema in the superficial lamina propria, and thinning of the intermediate lamina propria with thickening of the deep lamina propria. Additionally, the collagenous fibers in the vocal ligament were disorganized which, in extreme cases, resulted in fibrosis. Some age-related changes were sex specific, with females exhibiting increased thickness of the cover and males exhibiting decreased thickness.

It is important to note that not all voice disorders in elderly patients are the result of normal aging. Pathological conditions including benign vocal fold lesions, inflammatory disorders, and neurologic disorders can also cause dysphonia in this population (Woo 1992). As new onset dysphonia in the elderly may be a sign of an abnormal pathologic process, presbyphonia can be a diagnosis of exclusion (Mau 2010) with a somewhat imprecise definition. Classic presbyphonia typically presents with a gradual weakening of the voice. Patients may complain of limited projection, effortful phonation, and worsening voice quality over the course of a day (Kendall 2007). Visual examination may reveal vocal fold bowing due to muscle atrophy with persistent glottic insufficiency during phonation (Kendall 2007).
C.2 Neuromuscular and neurodegenerative diseases

Glottic insufficiency can occur in a wide variety of neurologic diseases, including multiple sclerosis (Rontal 1999), amyotrophic lateral sclerosis, syringomyelia (Willis 1968), myasthenia gravis (Mao 2001), Parkinson’s disease (Berke 1999), and stroke (Venketsubramanian 1999; Rubin 2007). Notably, greater than 70% of patients with Parkinson disease suffer from voice or swallow impairment, often due to glottic insufficiency (Berke 1999), and 30% of patients state these abnormalities are the most debilitating aspect of the disease (Hartelius 1994). Patients with neurologic disorders may already be at risk for aspiration due to a poorly coordinated swallow. In a study of five patients with aspiration and recurrent pneumonia due to neurologic disease, Broniatowski used paced glottic closure to improve vocal fold adduction and prevented further episodes of pneumonia in four of the five patients (Broniatowski 2010). Adding glottic insufficiency to the clinical picture of a patient with chronic neurologic disease should raise suspicion for swallowing dysfunction and possible aspiration pneumonia, the most common cause of death in patients with Parkinson disease (Beyer 2001; D’Amelio 2006).

C.3 Vocal fold scarring

Vocal fold scar is a challenging clinical problem with multiple causes and limited treatment options (Hirano 2005). Scarring can be congenital or acquired, with acquired causes including vocal abuse, chemical insult via smoking or reflux, thermal injury, iatrogenic trauma, and chronic inflammatory disease (Allen 2010). Post-surgical scarring can result in the epithelium adhering to the deeper layers of the vocal fold, disrupting the normal mucosal wave and creating glottic insufficiency (Arias 2010, Allen 2010). Patients commonly present with a
breathy, weak, and harsh voice and demonstrate asymmetric vibration with a glottal gap on exam (Hirano 2005; Benninger 1996).

Behavioral voice therapy can be helpful in preventing hyperfunctional phonation (Benninger 1996), but does not address the underlying histologic cause of the disorder (Hirano 2005). Collagen injection can eliminate the glottic gap and increase pliability of the lamina propria, but repeat injections are necessary and it is not well suited for large gaps (Ford 1987). Medialization thyroplasty can also be performed to close the gap, but does not affect the vibratory properties (Hirano 2005). In the future, pharmacologic and biochemical interventions may be most effective and could be useful in both prevention and treatment (Dailey 2006). Hepatocyte growth factor has antifibrotic activity and could be useful in scar therapy, as it promotes hyaluronic acid production and decreases collagen production (Hirano 2003).

**C.4 Vocal fold paralysis**

All but one of the intrinsic laryngeal muscles are controlled by the recurrent laryngeal nerve (RLN), a branch of the vagus nerve whose circuitous path provided the impetus for its name. Damage to this nerve, whether traumatic, iatrogenic, infectious, or associated with chronic disease, can cause vocal fold paralysis (VFP) and resultant glottic insufficiency.

A detailed explanation of the natural history of RLN injury and patterns of reinnervation is provided by Crumley (1994); a brief explanation is provided here. After complete transection of the RLN, the intrinsic muscles of the larynx are denervated and begin to undergo atrophy. After an acute phase characterized by degrading function, an intermediate phase occurs which is characterized by minor improvements in phonatory and deglutitive function. A chronic phase of recovery begins approximately four months after the injury; signs of clinical improvement are
often observed. Critical to understanding of reinnervation is synkinesis, or the phenomenon whereby adductor neurons innervate abductor muscles and abductor neurons innervate adductor muscles. While synkinesis prevents natural reinnervation from restoring normal function, any innervation is considered beneficial as it restores muscle tone. If no reinnervation occurs, denervation atrophy occurs (Martin 1989), resulting in total paralysis.

The majority of the literature review and series of studies will focus on VFP.

C.5 Impact on voice and swallowing

Socially, glottic insufficiency can impair patients’ ability to communicate with others, thus decreasing quality of life. Physiologically, glottic insufficiency results in a breathy voice and predisposition to airway compromise during swallowing.

The impact of glottic insufficiency is typically most pronounced during phonation. Patients complain of vocal fatigue, neck muscle tenderness, decreased projection, and decreased vocal range (Carroll 2012). If the glottal gap is significant, patients may develop secondary muscle tension dysphonia in an effort to achieve acceptable loudness (Belafsky 2002).

Glottic insufficiency can also have adverse effects on swallowing, as the ability of the larynx to protect the airway is inhibited. During swallowing, closure at the true vocal folds, false vocal folds, and aditus laryngis prevents entry of the bolus into the airway, while laryngeal elevation contributes to the generation of negative pressure which facilitates bolus passage into the esophagus. Maintaining a closed glottic system is required to ensure safe and effective swallowing (Eibling 1996; Carrau 1999). Across patients with glottic insufficiency, the severity of dysphagia can range from mild or even absent to severe with concerns for aspiration pneumonia (Bhattacharyya 2002). In a series of ninety-four patients reported by Carrau et al.,
seventy experienced aspiration which was not amenable to conservative compensatory strategies such as maneuvers and dietary changes; framework surgery including medialization thyroplasty and arytenoid adduction relieved aspiration in all but three of the seventy patients (Carrau 1999).

D. VOCAL FOLD PARALYSIS

“Vocal cord paralysis is a clinical finding of great interest to the otolaryngologist.”

-Robert Maisel and Joseph Ogura (1974)

D.1 Relevant anatomy

The recurrent laryngeal nerve (RLN) provides motor innervation to the thyroarytenoid, lateral cricoarytenoid, posterior cricoarytenoid, and interarytenoid muscles. The cricothyroid muscle is innervated by the superior laryngeal nerve (SLN). A lack of input to the lateral cricoarytenoid and thyroarytenoid muscles results in glottic incompetence with resultant breathy phonation and compromised laryngeal closure with susceptibility to aspiration. If innervation to the posterior cricoarytenoid is lost, the arytenoid tends to subluxate anteromedially as there is no posteriorly directed force to counter anterior movement (Crumley 1994).

The nuclei of the RLN axons are within the nucleus ambiguus in the lateral aspect of the rostral medulla. From the nucleus ambiguus, the RLN axons travel down the neck with the vagus nerve until separating at the subclavian artery on the right and the aortic arch on the left (Rubin 2007). The more inferior descent of the left RLN makes it susceptible to injury during thoracic surgery and is the side most commonly injured. In the neck alone, the right RLN has a more oblique course, exposing it and making it more vulnerable during procedures performed on the neck (Hollinshead 1982).
D.2 Etiology

The potential etiologies of VFP are diverse and, often times, a precise etiology is not determined. Iatrogenic injury during surgery on the neck or upper thorax is one of the more common causes. Rate of injury during thyroid surgery is approximately 0.5-2.0% for low-risk procedures and 5.0% for high-risk procedures such as those performed for malignancy, Graves’ disease, or autoimmune thyroiditis (Misiolek 2001; Cheng 2013). Reported rates of RLN palsy following anterior cervical spine surgery vary, but are typically approximately 5-10% (Jung 2005; Baron 2003). An incidence of 1-2% has been reported following coronary artery bypass graft (Martin-Hirsch 1995; Hahn 1970), while incidence after radical esophagectomy can be as high as 45% (Nishimaki 1998) (Hamdan 2002). Proximity of operative site and extent of procedure combine to account for the differences among these rates. Vocal fold immobility following endotracheal intubation is typically due to arytenoid dislocation rather than injury to the RLN, but abnormalities on electromyography can occur (Xu 2012). These abnormalities may be due to slight RLN injury associated with complete arytenoid dislocation, with the adductor branches being affected more easily than the abductor branches (Xu 2012).

VFP can also occur after trauma not associated with medical procedures. Reports of this in the literature consist largely of small case reports, such as that occurring after blunt trauma against a steering wheel in a car accident or a step after falling on a staircase (Brosch 1999; Levine 1995). In such cases, as in endotracheal intubation injury, the glottic insufficiency and dysphonia may be due to arytenoid dislocation rather than VFP. Careful examination of arytenoid movement which is typically greater in dislocation than VFP can distinguish the two entities (Sataloff 1994). As trauma sufficient to cause VFP is likely also sufficient to fracture the
laryngeal framework and compromise the airway, immediate concerns are the same as those for any severe trauma (i.e., maintenance of airway, normovolemia, and respiration, and prevention of infection if warranted) and voice quality is of secondary importance.

Infectious causes of VFP have also been documented. This represents a rare case where VFP can actually be treated and relieved with antimicrobial therapy. Interestingly, this has been reported multiple times in association with Lyme disease (Neuschaefer-Rube 1995; Schroeter 1988; Karosi 2010), a disorder which can also present with bilateral facial nerve palsy. Epstein-Barr virus and herpes simplex virus represent additional infectious etiologies (Feleppa 1981; Magnussen 1979).

A large proportion of cases are idiopathic. In a series of 176 patients with unilateral vocal fold paresis, Badia et al. reported that 46% had an unknown cause (Badia 2013). Importantly, the physician must investigate possible explanations for new onset paresis or paralysis, as it is often a sign of an underlying disorder (Tsikoudas 2012).

**D.3 Effects on laryngeal physiology**

VFP can impair breathing, swallowing, and vocal function (Havas 1999). In a prospective study of 87 patients by Bhattacharyya et al. using videofluoroscopy before and after vocal fold medialization, 31% exhibited penetration without aspiration and 23% exhibited aspiration (Bhattacharyya 2002). Penetration occurred most frequently during the swallow, while aspiration occurred both during and after the swallow with comparable frequency. Interestingly, medialization (injection with Gelfoam/Teflon or thyroplasty) in 23 patients did not have a significant effect on penetration-aspiration scale scores. Flint et al. found swallowing abnormalities in 60% of patients with VFP; in this group, medialization was generally effective
in eliminating aspiration and enhancing pharyngeal clearance (Flint 1997). Potential reasons for the discrepancy in findings in the two studies include the use of different assessments as well as different interventions. Importantly, the RLN also provides motor innervation to the inferior pharyngeal constrictor and cervical esophagus; loss of input after nerve injury can also adversely affect swallow function (Cunningham 1990).

Of all the effects VFP can have on physiology, effects on voice are typically most prominent and have thus been the focus of numerous basic science, translational, and clinical studies. The vocal folds oscillate via flow-induced sustained oscillation (Titze 2000). According to the myoelastic-aerodynamic theory of vibration, if the vocal folds are approximated, sufficient subglottal pressure can drive the folds apart, causing air to escape through the glottis (van den Berg 1958; Jiang 2000). The vocal folds then move laterally until elastic forces in the vocal fold tissue, particularly due to the elastin in the intermediate layer of the lamina propria, and negative pressure within the glottis cause the vocal folds to stop moving laterally and move medially. Coupling this mechanism with vocal tract inertance and time-delayed supraglottal pressure variation allows for sustained vocal fold oscillation (Titze 2000). In VFP, vocal fold approximation is difficult to achieve and a significantly increased effort is required to produce voice.

Voice associated with unilateral VFP is described as breathy, hoarse, and diplophonic (Crumley 1994). Importantly, increased aerodynamic energy is required to produce even a poor sounding voice. The larynx can be thought of as an energy transducer, transforming aerodynamic energy from the lungs into acoustic energy heard as speech (Jiang 2000). In glottic insufficiency, the process of energy transduction is inefficient. Air escapes through the incompetent glottis,
giving rise to a prominent DC component of airflow, increased phonation threshold pressure and flow, and a weak, breathy voice. Hyperadduction of the contralateral vocal fold may be present in an effort to improve vocal quality (Rubin 2007).

D.4 Clinical assessment

Evaluation of potential VFP, as with most ailments, should begin with a detailed history and focused physical exam. Key information to elicit includes onset characteristics, surgical history, recent trauma, recent infections, neurologic review of systems, and alcohol and tobacco history (Rubin 2007). The patient should be asked about the presence, duration, and severity of respiratory, deglutitive, or vocal complaints. Specific problems can include paralytic falsetto, impaired projection, air-wasting, inability to cough, and dyspnea on exertion due to the absence of normal laryngeal valving to regulate respiration (Richardson 2004). The falsetto may be due to the patient attempting to achieve glottic closure by contracting the cricothyroid muscles (Miller 2004; Stemple 2000).

The physical exam should include a standard head and neck exam including testing of cranial nerves, indirect and/or direct laryngoscopy, and subjective and quantitative voice evaluation. The most relevant finding is vocal fold immobility observed on laryngoscopy. Once identified, additional exams such as electromyography and physical exam findings can help elucidate the cause. Palatal deviation on cranial nerve exam would indicate a high vagal lesion, with the palate deviated away from the affected side. On laryngoscopy, several of the common causes of glottic insufficiency can be distinguished. Presence of symmetric bowing could indicate bilateral atrophy. In an elderly patient, this could be described as presbylaryngis. Sustained vocal approximation with local absence of the mucosal wave may indicate vocal fold
scar. Importantly, the airway should be evaluated for possible masses which may be impinging on or invading the RLN (Richardson 2004). If a proximal cause cannot be identified, imaging studies of the mediastinum or skull base may be warranted (Maisel 1974; Richardson 2004); however, in an evidence-based medicine review, Merati et al. found that the use of serum or radiographic studies to investigate idiopathic VFP has only grade C evidence (Merati 2006).

Functional voice testing can be helpful in the initial assessment of VFP, though may be more variable in evaluating treatment efficacy or patient progress over time due to variability in parameters across patients. Patients with VFP usually have a maximum phonation time (MPT) less than ten seconds and often even less than five (Richardson 2004). Acoustic analysis would likely reveal increased perturbation and also correlation dimension, a nonlinear dynamic parameter better suited for analysis of disordered voice (Zhang 2005). Perceptual analysis may demonstrate extreme roughness and breathiness (Schneider 2003).

Electromyography (EMG) can be valuable in the assessment of reinnervation, particularly if performed over time. EMG can be used to monitor ongoing changes in innervation (Bielamowicz 2004). Beginning at approximately 1.5-3 months after injury, recovery can be demonstrated by nascent units and polyphasic reinnervation potentials (Koufman 2000). If no evidence of reinnervation is found by three months, medialization may be warranted (Bielamowicz 2004).

**D.5 Surgical and behavioral treatment options**

Both surgical interventions and voice therapy have been recommended for the management of VFP. While surgery is performed frequently and discussed extensively in the literature, the role of voice therapy is less clear. Recent studies have reported benefits of voice
therapy (Khidr 2003; D’Alatri 2008; Mattioli 2011), which may be particularly valuable for those patients who are unwilling or unable to undergo an operation.

Even in patients who desire surgery, consultation with a speech pathologist may be beneficial to perform baseline functional voice measurements, educate the patient about basic laryngeal physiology, and discuss strategies to avoid aspiration or vocal abuse until the procedure can be performed (Miller 2004). Swallowing maneuvers such as a head turn toward the affected side (Logemann 1988) or a supraglottic swallow (Broniatowski 1999) may ensure safe swallowing (Miller 2004). Patients can also be cautioned against developing vocal hyperfunction and muscle tension dysphonia in an attempt to increase volume (Heuer 1997). Importantly, there may be a significant portion of patients who do not desire surgery. In a retrospective study by Heuer et al., thirteen of nineteen female and fourteen of twenty-two male patients chose not to undergo surgery after a trial of voice therapy. Most patients electing not to have an operation reported subjective improvement in vocal function (Heuer 1997).

Several surgical approaches to treating VFP have been proposed, including laryngeal reinnervation, injection laryngoplasty, medialization thyroplasty (MT), and arytenoid adduction (AA). Laryngeal reinnervation was pioneered by Crumley (Crumley 1986). Briefly, the ansa cervicalis is connected to the proximal recurrent laryngeal nerve. While this does not restore normal vocal fold movement, it can restore muscle tone, facilitate a more medial vocal fold position, and avoid potential side effects associated with a foreign implant (Paniello 2011). A delay of approximately six months is typical prior to procedural benefit and the procedure may be best suited for younger patients (Paniello 2011).
Injection laryngoplasty medializes a paralyzed vocal fold by increasing vocal fold volume. Wilhelm Brunings reported on the first vocal fold injection in 1911 (Brunings 1911). Commonly used materials include fat, collagen, micronized dermis, and calcium hydroxyapatite. Limitations of injection include absorption of the material into adjacent tissues (Rosen 1998) and difficulty revising incorrect injection volume or placement (Dedo 1992).

Type I thyroplasty, or MT, can be used in patients with more severe glottic insufficiency (Isshiki 1974). A window is cut in the thyroid lamina ipsilateral to the paralyzed vocal fold and an implant is inserted through the window, medializing the affected fold to the midline and allowing for vocal fold approximation. MT is the most commonly performed type of laryngeal framework surgery (Anderson 2003) and, in addition to VFP, can be used for vocal fold bowing (Lu 1998; Nassieri 2000), paresis (Lu 1998), and presbylaryngis (Isshiki 1975; Isshiki 1996). It has several benefits over IL, including permanence, ability to revise or remove the implant, and the ability to correct a more severe glottal gap. By inserting an implant, the membranous vocal fold structure is preserved and the procedure is reversible (Ford 1992). Injected material also tends to migrate through the laryngeal tissue over time, whereas solid implants maintain a stable shape and size and are less likely to undergo extrusion (Remacle 1988). Current implants can achieve effective medialization with a good postoperative voice outcome; however, none can be adjusted postoperatively without a second operation. Challenges associated with current MT have been the subject of numerous studies. Carving a Silastic implant (Netterville 1993) during surgery can result in suboptimal shaping and prolong procedural duration (Cummings 1993; Koufman 1986), resulting in increased intraoperative edema and decreased ability to judge intraoperative voicing accurately. Several alternatives to Silastic have been proposed, including
hydroxylapatite (Cummings 1993), the titanium vocal fold medializing implant (Friedrich 1999), and Gore-Tex (McCulloch 1998). These implants represent valuable innovations and can be used effectively to treat VFP; however, they cannot be modified postoperatively without a revision thyroplasty. Postoperative complications such as penetration and breathy phonation due to hypoadduction or dyspnea and pressed phonation due to hyperadduction are not uncommon; therefore, being able to adjust the degree of medialization postoperatively is desirable.

Dean et al. sought to address this issue with the titanium adjustable laryngeal implant (Dean 2001). Though promising, the implant was rather complex and requires six screws to secure the implant to the thyroid cartilage. Insertion of screws into the thyroid cartilage presents the risk of fracture, particularly in the elderly. Additionally, adjusting the degree of medialization would require accessing the original thyroplasty window where the screw is located, which would necessitate a second operation.

Arytenoid adduction (AA) is an additional treatment for VFP that is performed with MT, primarily indicated for patients with a wide glottal chink or superoinferior vocal fold asymmetry (Isshiki 1978). Sutures passed from the muscular process of the arytenoid through the thyroid cartilage can simulate the contractile forces of the lateral cricoarytenoid and thyroarytenoid muscles, medializing a paralyzed fold when tension is placed on the suture. The vocal process moves downward during adduction and can correct asymmetry by lowering the affected fold (Neuman 1994). When performed correctly, AA can produce dramatic improvement in laryngeal function. The superiority of combined MT-AA compared to MT has been demonstrated in several retrospective studies (McCulloch 2000; Abraham 2001; Mortensen 2009). MT is limited by an inability to close a wide posterior glottal chink and correct a difference in the horizontal
plane of the vocal folds. This is due to the posterior glottis and arytenoids residing outside the paraglottic space affected by the thyroplasty implant (McCulloch 2000).

E. QUANTITATIVE ANALYSIS OF VOICE PRODUCTION

Voice production is a complex physiological process requiring transduction of aerodynamic energy from the lungs into acoustic energy in the form of voice. Coordinated function of the nervous system, respiratory tract, and larynx is required to complete this process. Accordingly, voice disorders are multidimensional in nature, with different abnormalities affecting different aspects of the voice (Aboras 2010; Yu 2001). Despite this complexity, perceptual assessment is considered the gold standard of voice evaluation (Ma 2006); however, perceptual analysis can be unreliable when evaluating treatment efficacy or making comparisons across different voice disorders (Hakkesteegt 2008). Quantitative voice evaluation offers an objective method of quantifying laryngeal function.

E.1 Aerodynamic

Aerodynamic assessment evaluates the input to voice production (Baken 2000). Key to vocal fold vibration is subglottal pressure, the driving force of phonation. Aboras et al. measured both acoustic and aerodynamic parameters and found that subglottal pressure was the only measure predictive of a patient's self-perception of dysphonia (Aboras 2010). While subglottal pressure can be measured invasively via tracheal puncture (Isshiki 1964), it is preferable to measure it noninvasively. Smitheran and Hixon developed a method of measuring subglottal pressure via repeated productions of /pi/ into a mask while a tube is held at the lips. /p/ was chosen as it is a front bilabial plosive and is also the first plosive produced in development, while
/i/ was chosen as the vowel due to its front position (Smitheran 1981). Combined with airflow measured during the vowel (/i/), laryngeal airway resistance can be calculated by dividing subglottal pressure by airflow. While valuable, the task can be difficult for untrained subjects (Hertegard 1995) and simultaneous flow and pressure recordings can be difficult in young or disordered subjects (Smitheran 1981). An alternative to subject-controlled labial occlusion is occlusion of a tube using a mechanical shutter. This method has been used in numerous iterations in studies on both pulmonary and laryngeal physiology. Mead et al. used a rotating metal fin with occlusion duration of 100 milliseconds to measure airway resistance during respiration (Mead 1954). Jiang et al. used a balloon valve to interrupt subject airflow during phonation for 500 milliseconds and measure the phonation threshold pressure (Jiang 1999). This method removes the subjectivity of subject-controlled interruption and allows for estimation of phonation threshold pressure by calculating the difference between subglottal pressure and the supraglottal pressure at the moment phonation ceases during the interruption. In a study comparing intrasubject variability when measuring aerodynamic parameters using labial interruption and mechanical interruption, coefficient of variation for laryngeal resistance was significantly lower for mechanical interruption (Chapin 2011). Since the initial description of airflow interruption, it has since been modified by adding a known resistance and second valve to indirectly estimate subglottal pressure (Jiang 2006), increasing the size of the capacitor (Baggott 2007), consistently measuring subglottal pressure 150 milliseconds into the interruption (Hoffman 2009), and adding auditory and visual feedback during the trial (Hoffman 2013).

E.2 Acoustic
Quantitative acoustic measurements are commonly used to evaluate voice disorders. Frequently used acoustic measurements include perturbation parameters (jitter and shimmer), signal-to-noise or noise-to-harmonic ratio, and nonlinear dynamic parameters. Jitter and shimmer describe cycle-to-cycle variations in fundamental frequency or amplitude, respectively. While these parameters are useful (Dejonckere 2001), they are only valid for periodic or nearly periodic voice signals (Titze 1995). Nonlinear dynamic parameters of correlation dimension (D2) and second order entropy (K2) describe the complexity of a system and can be used to analyze the aperiodic signals characteristic of dysphonia (Herzel 1991; Titze 1993). To guide proper application of acoustic parameters, Titze presented a signal typing scheme (Titze 1995). Type 1 voice signals are nearly periodic, type 2 signals have strong modulations or subharmonics, and type 3 signals are aperiodic. Type 1 signals can be analyzed using perturbation parameters, type 2 signals can be analyzed using spectrograms or nonlinear parameters, and type 3 signals should be analyzed using perceptual observations or nonlinear parameters. While this scheme is helpful and encourages clinicians to avoid unreliable perturbation parameters when voice is severely disordered, it does not address voice signals with high-dimensional noise. Though current nonlinear parameters have improved quantitative acoustic assessment, they are negatively impacted by high dimensionality (Little 2007) due to computation time. Sprecher et al. proposed an update to the traditional signal typing scheme that divides previously designated type 3 signals into either type 3 (low-dimensional aperiodic signal) or type 4 (high-dimensional aperiodic signal). Type 4 signals are often interpreted as breathiness, such as that which occurs with glottic insufficiency. Importantly, all voices have some degree of high-dimensionality due
to the turbulence associated with the airflow jet needed to produce voice (Jiang 2002; Krane 2005).

**E.3 Vibratory**

Numerous modalities are available to evaluate changes at the glottis during vocal fold vibration, including indirect and direct methods. Indirect methods include photoglottography and electroglottography. Photoglottography is somewhat invasive and operates on the principle of transillumination. A light source and sensor are required, one of which is placed within the body, typically in the nasopharynx (Sonesson 1960). The sensor detects changes in light passage through the glottis which occur with vibratory cycles. A second indirect method is electroglottography, which measures electrical impedance across the glottis (Jiang 2000). Impedance is lowest during vocal fold contact and highest during maximal vocal fold displacement. While noninvasive and easy to perform, electroglottography can be unreliable if there are mucous strings across the glottis (Jiang 2000) or the electrodes are placed improperly.

Direct methods have garnered more interest in recent years and are used extensively in the clinic. Videostroboscopy uses a flashing light to piece together a vibratory cycle according to Talbot’s law of persistence of vision (Hirano 1993). According to this principle, a frame rate of only 30 frames per second can be used to visualize vocal fold vibration, a phenomenon occurring at a rate of 100-300 cycles per second. Importantly, this approach does not provide a detailed description of individual vibrations. If vibration is aperiodic, as in most cases of dysphonia, an inaccurate picture is formed. Patel et al. compared stroboscopy and qualitative high-speed digital imaging in patients with epithelial, subepithelial, or neuromuscular disorders and found that over 60% of stroboscopic data were not interpretable (Patel 2008). Stroboscopy does have several
advantages which make it useful clinically; it is inexpensive, widely available, can be used to make long recordings, and can be used to record video and audio signals simultaneously. An alternative to stroboscopy which provides greater detail on individual vibrations is high-speed videoendoscopy. Recordings are typically made at 4,000 frames per second, thus eliminating the key limitation of videostroboscopy (Eysholdt 1996; Hertegard 2003). High-speed video can be coupled with videokymography which analyzes displacement of a single pixel line along the glottis and allows for creation of a glottal waveform; this allows for quantification of mucosal wave parameters (Svec 2009; Jiang 2000) and has been used to identify voice disorders (Svec 2007). An alternative to videokymography which considers the entire vocal fold rather than a single pixel line is phonovibrography (Lohscheller 2008). Lohscheller et al. used phonovibrography to evaluate vocal nodules and unilateral vocal fold paralysis (Lohscheller 2008). The second derivative of the displacement waveform (acceleration) was best able to distinguish among normal subjects and the subjects with a disorder due to the presence of asymmetric acceleration.

F. VOCAL FOLD VIBRATION

Understanding normal vocal fold vibration and laryngeal physiology is essential if voice disorders are to be treated effectively. Key variables affecting vibration include tension, stiffness, glottal gap, and vocal fold contour.

F.1 Vocal fold tension and stiffness

Vocal fold stiffness is the effective restoring force in the transverse plane per unit of displacement; this is primarily regulated by vocal fold length and is directly proportional to vocal
fold tension (Titze 2000). Vocal fold length is governed by contraction of the cricothyroid muscles, which are innervated by the external branch of the superior laryngeal nerve. The cricothyroid muscle is comprised of three bellies: the oblique, vertical, and horizontal (Mu 2009). Contraction of the muscle causes anteroinferior rocking of the thyroid cartilage and lengthening of the vocal folds (Sulica 2004). Unilateral paralysis of the cricothyroid muscle can result in a breathy, low-pitched voice with loss of frequency range (Roy 2009).

The thyroarytenoid muscle also plays a role in determining vocal fold tension and thus fundamental frequency. Importantly, these two muscles can be controlled independently as they are innervated by separate branches of the vagus nerve. Three combinations of muscle activity are possible, with each having different effects on phonation (Titze 2000) based on the body-cover theory of vibration (Hirano 1974). If the cricothyroid contracts and the thyroarytenoid is inactive, the vocal fold lengthens, the stiffness of the body and cover is increased, and the fundamental frequency is increased. If the cricothyroid remains inactive and the thyroarytenoid contracts, vocal fold length and stiffness of the cover decrease while stiffness of the body increases; this typically results in a decrease in the fundamental frequency. If both the cricothyroid and thyroarytenoid contract, the fundamental tends to increase slightly. Optimal control over pitch range is accomplished by relaxing the thyroarytenoid slowly as cricothyroid contraction is increased (Titze 2000).

**F.2 Prephonatory glottal width**

Consideration of prephonatory glottal width is of the utmost importance when evaluating disorders characterized by glottic insufficiency. Changes in this variable affect laryngeal airway resistance and cause predictable changes on laryngeal aerodynamics. Phonation threshold flow,
the minimal airflow required for sustained vocal fold oscillation (Jiang 2007), increases with increasing glottal gap (Hottinger 2007). Phonation threshold pressure tends to be elevated with large changes in the glottal gap, though small changes can result in no change (Hottinger 2007). Importantly, the presence of a glottal gap introduces a direct current component to airflow, resulting in breathy phonation and high-dimensional chaotic vibration (Sprecher 2010). This can also be quantified using the open quotient, with values greater than 0.7 (meaning vocal fold contact occurs for no more than 30% of the vibratory cycle) corresponding to a breathy voice (Titze 2000).

**F.3 Vocal fold contour**

The importance of vocal fold contour can be appreciated by visiting a middle school classroom and listening to the changing voices of adolescent males. During puberty, the thyroarytenoid muscle increases in bulk, creating a more rectangular glottis. More of the vocal fold body is involved in vibration, resulting in a voice which has a richer timbre (Titze 2000). As the shape of the laryngeal instrument changes, so too must the method by which it is used. During the transition period, mastering control of the rectangular glottis is challenging and vibration mode can change inadvertently, resulting in a voice “crack” (Titze 2000).

Though a critical aspect of vibratory control, the effect of vocal fold contour has been relatively understudied, possibly due to the difficulty viewing the medial surface of the vocal folds in a living human (Mau 2012). Though human studies on this topic are limited, modeling studies have provided significant insight. Titze modeled three primary glottal shapes: convergent, divergent, and rectangular (Titze 2000). Mau et al. demonstrated the ability to manipulate vocal fold contour via vocal fold injection in excised larynges (May 2012). Such
modifications may be desirable in persons with glottic insufficiency, particularly that caused by vocal fold atrophy with corresponding excessively convergent glottis. A rectangular prephonatory glottal shape is associated with low phonation threshold pressure (Chan 1997) and high vocal efficiency (Titze 1979); however, excessive medialization of the glottis without modification of the subglottis can cause increased turbulent airflow (Grisel 2010).

G. STATEMENT OF THE PROBLEM

Correct implementation of thyroplasty with or without an arytenoid adduction can provide a permanent treatment for many patients with glottic insufficiency; however, there are several clinical scenarios where new approaches could be beneficial. First, persons whose professions have significant vocal demands often require multiple fine-tuning procedures before an optimal phonatory outcome is achieved (Anderson 2003). These fine tuning procedures involve increasing or decreasing the degree of medialization, with each revision requiring an additional surgery. An implant which could be adjusted postoperatively without the need for an additional operation could decrease financial and temporal costs. Secondly, patients with disorders that have a progressive component such as presbylaryngis may require increases in the degree of medialization over time (Woo 2001). These patients could similarly benefit from an implant which can be modified postoperatively. Third, as with most surgical procedures, probability of a desirable outcome is related to surgeon experience (Rosen 1998). The ability to adjust degree of medialization postoperatively may allow general otolaryngologists who do not regularly perform thyroplasty to still achieve a positive outcome. This is a potentially desirable feature for experienced laryngologists as well. In a case series from Woo et al. of patients with
failed MT, 15 of 20 patients presented postoperatively with breathy dysphonia (Woo 2001), indicative of insufficient medialization which then required a revision thyroplasty. Lastly, patients with significant vertical vocal fold asymmetry or a prominent glottal chink require manipulation of the arytenoid; however, accessing the posterior larynx and manipulating the muscular process of the arytenoid is difficult (Slavit 1992; Mahieu 1989; Slavit 1994; Woo 2000). These patients would benefit from a new procedure which can be used to manipulate the arytenoid via an anterior approach.

When developing new treatment devices and approaches, it would be desirable to design them in such a way that they could be performed in a minimally invasive fashion without the need for a large neck incision. Scars can adversely affect patient appearance, psyche, and quality of life (Durani 2009). Additionally, socioeconomic factors favor office procedures over those performed in an operating room when feasible (Zeitels 2007). A minimally invasive, office-based procedure would also facilitate routine application of surgical medialization to disorders beyond severe vocal fold paralysis, including presbylaryngis and vocal fold scar.

H. GAPS IN KNOWLEDGE AND STUDIES TO ADDRESS THEM

H.1 Does adding arytenoid adduction to medialization thyroplasty improve phonatory outcome?

Each medialization procedure has advantages and disadvantages. Injection laryngoplasty is quick, low cost, and can be performed in the office; however, it is not permanent. Medialization thyroplasty provides effective permanent medialization of the membranous vocal fold; however, it requires an operation and cannot reliably alter arytenoid position. Arytenoid
adduction can correct a posterior glottic gap as well as vertical vocal fold asymmetry; however, it is technically challenging and associated with increased morbidity. Retrospective studies comparing these procedures and determining if adding arytenoid adduction to thyroplasty is beneficial, but patient groups are typically separate with different characteristics. An excised larynx experiment could offer an objective evaluation of these procedures and determine if arytenoid adduction has any added benefit after thyroplasty. Unilateral VFP was simulated in two sets of excised larynges, one undergoing injection laryngoplasty and the other undergoing thyroplasty and arytenoid adduction. Aerodynamic, acoustic, and videokymographic measurements were obtained. I hypothesized that adding arytenoid adduction would be beneficial in cases where a large glottic gap is present, and that injection and thyroplasty would lead to similar outcomes.

**H.2 What is the effect of the titanium vocal fold medializing implant on quantitative phonatory parameters?**

Thyroplasty with the titanium vocal fold medializing implant has been shown to be effective based on subjective indices, measurements of glottal gap, and postoperative respiratory studies (Friedrich 1999; Schneider 2003); however, its effect on quantitative voice parameters and mucosal wave vibratory characteristics as measured using high-speed video is unknown. Thyroplasty with the titanium implant was performed on a set of larynges with simulated unilateral VFP. Aerodynamic, acoustic, and videokymographic measurements were obtained. I hypothesized that thyroplasty with the titanium vocal fold medializing implant would decrease threshold aerodynamic and perturbation parameters, increase signal-to-noise ratio, and preserve mucosal wave amplitude.
H.3 Can real-time quantitative voice analysis be used to guide arytenoid adduction?

Subjective clinician-based assessment of intraoperative patient phonation is used to determine the appropriate degree of arytenoid rotation when performing arytenoid adduction. Using real-time measurements of vocal efficiency and perturbation parameters may help determine the optimal degree of arytenoid rotation. Thyroplasty with arytenoid adduction was performed on a set of larynges with simulated unilateral VFP. Real-time measurements of vocal efficiency, percent jitter, and percent shimmer were obtained while rotating the arytenoid. I hypothesized that vocal efficiency would increase and perturbation parameters would decrease until optimal position was reached, at which point vocal efficiency would begin to decrease and perturbation parameters would increase. This point would coincide with optimal phonatory outcome as evaluated using other aerodynamic, acoustic, and videokymographic measurements.

H.4 Can vocal fold medialization be accomplished with an implant that could be modified postoperatively?

An implant which could be adjusted postoperatively without the need for a revision thyroplasty could fill a significant gap in the current management of glottic insufficiency. An inflatable silicone balloon could provide a range of degrees of medialization, and a tube extending from the implant could be placed close to the skin surface to allow for postoperative adjustment. A custom made spherical silicone balloon implant was inserted into larynges with simulated unilateral VFP and filled until medialization was achieved. This condition was compared to simulated paralysis to determine if treatment significantly improved phonation as well as simulated normal to determine if treatment restored normal voice production. I
hypothesized that thyroplasty with the adjustable balloon implant would provide effective medialization and restore phonatory parameters to approximately normal levels.

H.5 Does incorporation of a variety of parameters improve the ability to identify glottic insufficiency and tension asymmetry?

Perceptual assessment is considered the gold standard of voice evaluation (Ma 2006) but can be imprecise when making comparisons across groups or over time (Hakkesteegt 2008). The ability to identify voice disorders may be improved by including a variety of quantitative, objective parameters in the evaluation. Aerodynamic, acoustic, and videokymographic measurements represent potentially useful candidates, but are not always performed. Analysis of any single parameter individually may not be valuable, but collective analysis of a variety of parameters likely would be. Such analysis can be facilitated by pattern recognition techniques such as artificial neural networks which use nonlinear statistical analysis to classify data into groups. I used a multilayer perceptron to classify data collected from excised larynges simulating normal, glottic insufficiency, and tension asymmetry using aerodynamic, acoustic, and videokymographic parameters. I hypothesized that classification accuracy would be highest when including all three groups of parameters.

H.6 Can arytenoid adduction be performed from an anterior approach?

Arytenoid adduction can produce dramatic improvements in voice production but is technically challenging (Woo 2000) and thus not performed as frequently as it is warranted (Damrose 2003). Addressing the arytenoid from an anterior approach may make the procedure significantly easier while not sacrificing procedural effect. Gore-Tex suture attached to curled wire with a hook could be passed through the thyroid cartilage or cricothyroid membrane and
attach to the soft tissue surrounding the muscular process of the arytenoid, allowing one to manipulate the arytenoid and thus vocal fold without accessing the posterior larynx. Traditional and anterior arytenoid adduction were performed in excised larynges. I hypothesized that phonatory outcome for the two procedures would be comparable.

**H.7 Can vocal fold medialization be achieved using an inflatable implant inserted via a minithyrotomy?**

Data from our initial experiment on the silicone adjustable balloon implant demonstrate its potential as a new implant for thyroplasty; however, the spherical shape required it be inserted via a traditional thyroplasty window and stabilized by a metal frame and resulted in a residual posterior glottic gap. A wedge-shaped implant may better conform to the natural shape of the vocal fold, and could possibly also be inserted via a minithyrotomy approach. I hypothesized that a wedge-shaped silicone balloon inserted via a minithyrotomy could achieve vocal fold medialization and restore phonatory parameters to approximately normal levels.

**I. REFERENCES**


CHAPTER 2

Multi-parameter comparison of injection laryngoplasty, medialization laryngoplasty, and arytenoid adduction in an excised larynx model

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ABSTRACT

Objective: Evaluate the effect of injection laryngoplasty (IL), medialization laryngoplasty (ML), and ML combined with arytenoid adduction (ML-AA) on acoustic, aerodynamic, and mucosal wave measurements in an excised larynx setup.

Methods: Measurements were recorded for eight excised canine larynges with simulated unilateral vocal fold paralysis (UVFP) before and after vocal fold injection with Cymetra. A second set of eight larynges was used to evaluate medialization laryngoplasty using a Silastic implant without and with arytenoid adduction.

Results: IL and ML led to comparable decreases in phonation threshold flow (PTF), phonation threshold pressure (PTP), and phonation threshold power (PTW). ML-AA led to significant decreases in PTF (p=0.008), PTP (p=0.008), and PTW (p=0.008). IL and ML led to approximately equal decreases in percent jitter and percent shimmer. ML-AA caused the greatest increase in signal to noise ratio (SNR). ML-AA discernibly decreased frequency; a clear trend was not observed for IL or ML. IL significantly reduced mucosal wave amplitude, while both ML and ML-AA increased it. All procedures significantly decreased glottal gap, with the most dramatic effects observed after ML-AA.
**Conclusions:** ML-AA led to the greatest improvements in phonatory parameters. IL was comparable to ML aerodynamically and acoustically, but caused detrimental changes to the mucosal wave. Incremental improvements in parameters recorded from the same larynx were observed after ML and ML-AA. To ensure optimal acoustic outcome, the arytenoid must be correctly rotated. This study provides objective support for the combined ML-AA procedure in tolerant patients.

**INTRODUCTION**

The recurrent laryngeal nerve (RLN) innervates the intrinsic laryngeal muscles necessary for vocal fold adduction. Injury to the RLN, typically traumatic or iatrogenic, can cause unilateral vocal fold paralysis (UVFP) which impairs voice, swallowing, and breathing function (Havas 1999). Numerous surgical interventions are used to medialize the affected fold with the aim of improving laryngeal function by decreasing glottal gap. Two common approaches include injection laryngoplasty (IL) and laryngeal framework surgery.

Vocal fold injection using fat, collagen, micronized dermis, or hydroxyapatite (Brandenburg 1992; Ford 2004; Bock 2007; Rosen 2004) medializes a paralytic vocal fold by increasing vocal fold volume. Injections are less invasive than laryngeal framework surgery and can be performed as an outpatient procedure under local anesthesia (Ford 2004). Though convenient, there are several limitations to IL including possible decreased mucosal wave amplitude if vocal fold stiffness is increased (Gardner 1991), gradual absorption of the injected material into surrounding tissues (Rosen 1998), and irreversibility (Dedo 1992). Early injections used Teflon which has a tendency to form granulomas and is difficult to remove once injected...
Fat, which has a viscosity close to that of vocal fold tissue, was later developed as an injection material (Chan 1998). Currently, micronized dermis is a widely used material that has been reported to improve voice to the same degree as type I thyroplasty (Lundy 2003; Morgan 2007). Pearl et al. reported significant improvements in jitter and shimmer as well as habitual phonation time and airflow after injection of micronized AlloDerm (Pearl 2002); however, Cymetra is a temporary injection agent and its small particles are susceptible to phagocytosis, leading to reabsorption (Sclafani 2000) and the need for repeat injections.

Medialization laryngoplasty (ML), introduced by Isshiki, improves vocal quality in patients affected by UVFP (LaBlance 1992; Sasaki 1990) and has several reported advantages over IL. Insertion of an implant allows for preservation of the mucosal wave (Ford 1992). Implants also retain their size over time and do not carry the risk of reabsorption into tissues (Remacle 1988). An implant can also be removed easier than injected material, though implant insertion can lead to permanent fibrosis in the paraglottic space as well as changes to the cricoarytenoid joint (Conoyer 2006). However, thyroplasty has several disadvantages not encountered by IL. Submucosal hemorrhage as well as implant extrusion can occur (Tucker 1993). Silicone implants must be carved during surgery, increasing operation time. Suboptimal shaping can hinder potential improvements in voicing, breathing, and swallowing (Koufman 1986; Cummings 1993; Montgomery 1997).

Though thyroplasty is an effective treatment for UVFP, it is limited by an inability to close a wide posterior glottal gap or correct a difference in the horizontal plane of the two vocal folds (McCulloch 1998). Coupling medialization laryngoplasty with arytenoid adduction (ML-AA) has been shown to overcome these limitations and improve vocal outcomes (McCulloch...
Despite the benefit of the procedure, AA is performed less frequently than it should due to increased technical demands and time (Isshiki 1991; Rosen 1998). Overrotation of the arytenoid, apparent shortening of the vocal fold, or a failure to achieve vertical alignment between the folds can occur, mitigating procedural efficacy and compromising voice quality (Isshiki 1991; Slavit 1992). The benefits of ML-AA are also not well defined (Chester 2003; Noordzij 1998). Many studies evaluating the benefit of arytenoid adduction have compared post-procedure outcomes to patients only receiving thyroplasty, rather than analyzing the added benefit of performing arytenoid adduction after thyroplasty in the same patient (Chester 2003).

Determining the optimal treatment for UVFP remains a clinical challenge. Excellent and persistent voice improvement at three months has been reported in 88% of patients following micronized dermis injection (Damrose 2003). Sclafani et al. reported on the molecular benefits of micronized dermis injection, including fibroblast proliferation with collagen deposition (Sclafani 2000). As IL is a less invasive and less expensive procedure to perform than ML, it is important to reassess which procedure is most beneficial for patients with UVFP.

This study quantified the effects of IL, ML, and ML-AA on mucosal wave, acoustic, and aerodynamic properties of phonation in an excised larynx. This controlled setting allowed for precise and repeatable measurements of all parameters, as well as analysis of the additive benefits offered by AA.

**MATERIALS AND METHODS**

_Larynges_
Sixteen larynges were excised postmortem from canines sacrificed for non-research purposes according to the protocol described by Jiang and Titze (Jiang 1993). Canine larynges are much more widely available at our institution than human larynges. As the size and histological properties of the canine and human larynx are similar (Noordzij 1998), it is an appropriate model for studying human laryngeal physiology. Larynges were examined for evidence of trauma or disorders; any larynges exhibiting trauma or disorders were excluded. Following visual inspection, larynges were frozen in 0.9% saline solution. The sixteen larynges were divided into two groups: (1) injection laryngoplasty (IL) and (2) medialization laryngoplasty (ML) without and with arytenoid adduction (ML-AA).

**Apparatus**

Prior to the experiment, the epiglottis, corniculate cartilages, cuneiform cartilages, and ventricular folds of the larynx were dissected away to expose the true vocal folds. The superior cornu and posterosuperior part of the thyroid cartilage ipsilateral to the normal vocal fold were also dissected away to facilitate insertion of a lateral 3-pronged micrometer into the arytenoid cartilage. The larynx was mounted on the apparatus (figure 1) as specified by Jiang and Titze (Jiang 1993). A metal pull clamp was used to stabilize the trachea to a tube connected to a pseudolung which served as a constant pressure source. Insertion of one
3-pronged micrometer in the arytenoid cartilage ipsilateral to the dissected thyroid cartilage (figures 2A, 3A) allowed for adduction of one vocal fold, simulating UVFP in the unadducted vocal fold as in Czerwonka et al. (Czerwonka 2009) and Inagi et al. (Inagi 2002). Methodological consistency was maintained by always adducting the contralateral arytenoid (simulated normal) to the midline. Micrometer positioning remained across sets of trials within the same larynx. Tension on the vocal folds and control of vocal fold elongation was accomplished by attaching the superior anteromedial thyroid cartilage, just inferior to the thyroid notch, to an anterior micrometer. Vocal fold elongation and adduction remained constant for all trials.

The pseudolung used to initiate and sustain phonation in these trials was designed to simulate the human respiratory system. Pressurized airflow was passed through two Concha Therm III humidifiers (Fisher & Paykel Healthcare Inc., Laguna Hills, California) in series to humidify and warm the air. The potential for dehydration was further decreased by frequent application of 0.9% saline solution between trials. Airflow was controlled manually and was measured using an Omega airflow meter (model FMA-1601A, Omega Engineering Inc., Stamford, Connecticut). Pressure measurements were taken immediately before the air passed into the larynx using a Heise digital pressure meter (901 series, Ashcroft Inc., Stratford, Connecticut).

Acoustic data were collected using a Sony microphone (model ECM-88, Sony Electronics Inc., New York, New York) positioned at a 45° angle to the vertical axis of the vocal
tract. The microphone was placed approximately 10 cm from the glottis to minimize acoustic noise produced by turbulent airflow. Acoustic signals were subsequently amplified by a Symetrix preamplifier (model 302, Symetrix Inc., Mountlake Terrace, Washington). A National Instruments data acquisition board (model AT-MIO-16; National Instruments Corp, Austin, Texas) and customized LabVIEW 8.5 software were used to record airflow, pressure, and acoustic signals on a personal computer. Aerodynamic data were recorded at a sampling rate of 200 Hz and acoustic data at 40,000 Hz. Experiments were conducted in a triple-walled, sound-proof room to reduce background noise and stabilize humidity levels and temperature.

The vocal fold mucosal wave was recorded for approximately 200 milliseconds per trial using a high-speed digital camera (model Fastcam-ultima APX; Photron, San Diego, CA). Videos were recorded with a resolution of 512 x 256 pixels at a rate of 4000 Hz.

Experimental Methods

Trials were conducted as a sequence of 5 second periods of phonation, followed by 5 second periods of rest. Five trials were performed for each condition. During each trial, airflow passing through the larynx was increased gradually and consistently until the onset of phonation. All procedures were performed by the same author (MRH) under the supervision of the senior author (TMM). Total experiment time was fifteen minutes for the larynges receiving IL and thirty minutes for the larynges receiving ML-AA. Larynges were thoroughly hydrated with saline solution between trials and between sets of trials to eliminate any potentially confounding effects of dehydration.

IL was performed using Cymetra micronized AlloDerm (LifeCell Corporation, Branchburg, NJ). Cymetra was prepared according to manufacturer specifications by diluting the
micronized dermis with 1.7 cc saline. The solution was mixed in two syringes by pushing the syringe plungers back and forth in a continuous motion. Prior to injection, air was expelled from the solution. Approximately 0.3 - 0.5 cc were injected at each of two sites on the vocal fold: just lateral to the vocal process and the lateral aspect of the midpoint of the vocal fold. A 1.5 inch 23-gauge needle (Becton, Dickinson, and Company, Franklin Lakes, NJ) was used at a depth of 2-4 mm. The amount injected was dependent upon the size of the larynx and was determined by minimizing the aerodynamic power necessary to initiate phonation. Caution was taken to avoid overinjection which could lead to vocal fold bowing or excessive medialization at the anterior commissure.

ML was performed using a Silastic implant (Dow Corning Corporation, Midland, MI). The implant was inserted through a 6 x 11 mm thyroplasty window in the thyroid cartilage ipsilateral to the paralyzed vocal fold. Optimal degree of medialization was determined empirically by minimizing the aerodynamic power necessary to initiate phonation.

AA was performed after a set of trials was conducted analyzing the effect of ML. The procedure was performed according to the clinical descriptions by Isshiki (Isshiki 1978). One suture was passed with a needle from the muscular process of the arytenoid anteriorly through the paraglottic space through the thyroid cartilage just lateral to the anterior commissure and the second inferior to the cartilage was tightened to rotate the arytenoid and adduct the simulated paralyzed fold. The optimal degree of rotation was determined by minimizing the aerodynamic power needed to initiate phonation while preserving acoustic quality.

Data Analysis
Phonation was evaluated before and after each procedure. Airflow and pressure at the phonation onset were recorded as the phonation threshold flow (PTF) and phonation threshold pressure (PTP), respectively. Phonation threshold power (PTW) was calculated as the product of these values. PTF, PTP, and PTW were determined manually using customized LabVIEW 8.5 software. Phonation onset was determined spectrographically; airflow and pressure at this time were recorded as PTF and PTP.

Measured acoustic parameters included frequency, signal-to-noise ratio (SNR), percent jitter, and percent shimmer. Acoustic signals were trimmed using GoldWave 5.1.2600.0 (GoldWave Inc., St. John’s, Canada) and analyzed using Computerized Speech Lab (CSpeech) software (Madison, WI).

High speed video recordings of the mucosal wave were analyzed using a customized MATLAB program (The MathWorks, Natick, MA). Vibratory properties of each of the four vocal fold lips (right-upper, right-lower, left-upper, left-lower) were quantified via digital videokymography (VKG). Threshold-based edge detection, manual wave segment extraction, and non-linear least squares curve fitting using the Fourier Series equation were applied to determine the most closely fitting sinusoidal curve. This curve was used to derive the amplitude and phase difference of the mucosal wave of each vocal fold lip, both before and after treatment. Phase difference was calculated as the phase difference between the right upper and left upper vocal fold lips. Mucosal wave amplitude was calculated as the average of the amplitudes of the upper and lower paralyzed vocal fold lips. While only relative rather than absolute values could be obtained due to current technological limitations, this was sufficient for pre-/post-treatment comparisons.
Statistical analysis

Paired t-tests were performed to determine if IL, ML, and ML-AA had significant effects on the parameters of interest compared to the larynx with simulated UVFP. A paired t-test was also performed to determine if AA had a significant effect after ML. If data were not normal according to a Shapiro-Wilk test or did not display equal variance according to a Levene’s test, a Wilcoxon-Mann-Whitney paired rank sum test was performed. Tests were two-tailed and a significance level of \( \alpha=0.05 \) was used.

To analyze the comparative efficacy of the procedures, percent change of each parameter after treatment was calculated. These percent changes were then compared using an independent samples t-test. If data did not meet the assumptions for parametric testing, a Wilcoxon-Mann-Whitney rank sum test was performed. Tests were two-tailed with a significance level of \( \alpha=0.05 \).

RESULTS

Aerodynamics

Summary

Summary aerodynamic data and statistics are presented in tables I and II. IL, ML, and ML-AA significantly decreased PTF (\( p=0.007 \); \( p=0.003 \); \( p=0.008 \)), while only ML-AA had a significant effect on PTP (\( p=0.008 \)) and PTW (\( p=0.008 \)).
No significant differences were observed in percent change between injection and thyroplasty (PTF: p=0.766; PTP: p=0.773; PTW: p=0.639). The addition of AA led to significantly greater changes as compared to IL in PTF (p=0.008), PTP (p=0.008), and PTW (p=0.008) (figure 4).

Acoustics

Summary acoustic data and statistics are presented in tables III and IV. IL, ML, and ML-AA decreased perturbation measures of percent jitter and percent shimmer. IL decreased percent jitter significantly (p=0.017); the decrease in percent shimmer approached significance (p=0.079). ML significantly decreased percent jitter (p=0.03) and shimmer (p=0.043). The addition of AA further decreased percent jitter, though not significantly (p=0.085). IL, ML, and ML-AA also increased SNR (p=0.078; p = 0.338; p=0.042). Neither IL (p=0.912) nor ML (p=0.747) had an effect on frequency. There was a discernible decrease in frequency after ML-AA (p=0.059).

IL and ML had comparable effects on both percent jitter (p=0.853) and percent shimmer (p=0.670). A discernible difference was observed, however, for SNR (p=0.161). Adding AA led to greater improvement in perturbation measures compared to IL, though neither reached significance (percent jitter: p=0.105; percent shimmer: p=0.130) (figure 4).

Mucosal wave

Figure 5. Kymograms derived from high speed video recordings of vocal fold vibration with simulated vocal fold paralysis (A, lower curve) and after injection laryngoplasty (B).
Summary mucosal wave data and statistics are presented in tables V and VI. All procedures significantly decreased glottal gap (p<0.001). IL also decreased inter-fold phase difference (p=0.042) and amplitude of the paralytic fold (p=0.002). Decreased amplitude can be observed on the videokymogram derived from the high speed video recording (figure 5). ML did not have significant effects on either amplitude (p=0.879) or phase difference (p=0.116). The addition of AA to ML significantly decreased glottal gap (p=0.004) and discernibly increased amplitude (p=0.128).

ML improved mucosal wave amplitude (p=0.006) and phase difference (p=0.05) significantly more than IL. ML-AA decreased phase difference between the right and left vocal folds significantly more than ML alone (p = 0.008). Incremental increases in mucosal wave amplitude can be seen in kymograms after ML and after ML-AA (figure 6) (figure 4).

**DISCUSSION**

This study performed a quantitative evaluation of IL, ML, and ML-AA to determine the effect of each on various parameters of phonation. Doing so in a controlled excised larynx setting with easily repeatable conditions decreased potential variability which may arise when conducting research on human subjects. Both ex vivo and in vivo canine larynges have been used previously to study interventions for vocal fold paralysis (Noordzij 1998; Czerwonka 2009; Inagi 2002). There are several anatomical differences between the human and canine larynx. The thyroid and cricoid cartilages and more angulated and not as tall
in the canine larynx, and there is no well-defined vocal ligament (Noordzij 1998). These differences did not negatively impact the procedures that were evaluated.

IL and ML had significant effects on PTF, but not PTP. The added aerodynamic benefit of AA was evident, significantly decreasing PTF, PTP, and PTW. This change could be attributed to the decreased posterior glottal gap following adduction. Such a decrease would decrease PTF, a parameter dependent upon the cube of neutral glottal half-width (Jiang 2007), and increase ease of phonation, promoting more efficient voicing. Though previous studies have measured the effect of different procedures on PTP, this is the first comparison using PTF. Measuring PTF offers an improved method of analyzing aerodynamic improvement after treatment for UVFP, as PTF is more sensitive than PTP to changes in glottal abduction (Hottinger 2007). This is also the first study analyzing PTW, a comprehensive threshold aerodynamic parameter proposed by Jiang and Tao (Jiang 2007). This may be the optimal parameter to use when evaluating post-treatment laryngeal aerodynamics at the phonation threshold, as it encompasses both pressure and airflow.

As phonation tokens were taken at the phonation threshold, differences in frequency can be attributed to differences in PTP. ML-AA had the lowest PTP; accordingly, it also had the lowest frequency. Restoration of vocal fold contact via medialization of the paralyzed fold led to decreases in both percent jitter and shimmer. Interestingly, the addition of AA led to an additional significant decrease in percent jitter, while slightly increasing percent shimmer. Three of the eight larynges undergoing ML-AA had much higher percent jitter (4.47 ± 2.27) and percent shimmer (34.91 ± 10.87) than the other five (percent jitter: 1.18 ± 0.89; percent shimmer: 4.83 ± 3.69). Improper rotation of the arytenoid leading to vocal fold hypo- or hyperadduction in
these larynges could have potentially led to this increase in perturbation measures and compromised acoustic quality. Posterior glottal gap in these larynges was higher (48.20 ± 22.97) than in the five larynges achieving superior acoustic outcomes (15.6 ± 9.58), indicating possible hypoadduction. Increased SNR across treatments can be attributed to decreased flow, or noise, required for phonation as well as improved acoustic sound, the signal. Improvement could be seen most dramatically with ML-AA, which resulted in an average increase greater than 300%. The three larynges exhibiting increased perturbation parameters also had the lowest SNR, likely due to decreased signal power rather than increased noise power.

Though IL is an effective clinical procedure that has benefits of convenience and relatively minimal invasiveness, its effect on the mucosal wave is detrimental (figure 5). IL led to improvements comparable to ML in acoustics and aerodynamics, but ML increased mucosal wave amplitude of the paralyzed fold while IL significantly decreased it. Analyzing other injection materials, such as fat which has the same viscosity as the vocal fold (Chan 1998), may yield different results; however, a portion of these substances may be absorbed by the surrounding tissue over time (de Souza Kruschewsky 2007; Brandenburg 1996; Zaretsky 1995).

Though ML-AA produced the best results in this study and is often beneficial for patients with posterior glottal chink, it is not appropriate for all patients. Not all patients are amenable to the increased operative time required to perform AA, such as those with iatrogenic UVFP stemming from complications during cardiothoracic surgery or those with severe aspiration that may not be able to remain supine for extended periods of time (McCulloch 2000). Patients with aspiration that can tolerate the procedure, however, may experience improvement after AA (Carrau 1992). Selecting the proper procedure requires consideration beyond voice improvement.
Incremental improvements in phonatory parameters after ML and ML-AA provide support, however, for the added procedure in patients who can tolerate it.

The experimental design allowed for easy and direct evaluation of the added benefits of performing AA. The benefits on aerodynamics and SNR, attributable to a decreased posterior glottal gap, were significant. As could be expected, ML-AA produced the most dramatic improvement in phonatory parameters (figure 4). Restoration of a normal mucosal wave, indicated by symmetric and periodic sinusoidal functions with sustained inter-vocal fold contact between cycles (Zhang 2009), also occurred in some larynges after AA (figure 6). However, as demonstrated by acoustic parameters, under- or overrotation of the arytenoid, common complications of AA, can sacrifice procedural outcome and should be avoided. Real-time intraoperative voice analysis may provide one means of preventing improper rotation and ensuring optimal voice quality. Future studies could use quantifiable acoustic and mucosal wave parameters to optimize degree of arytenoid rotation while performing AA.

An excised larynx setting offers the benefits of repeatable conditions, but confirming the results of this study in humans would be beneficial. Applying the aerodynamic and mucosal wave analyses used in this study may be of interest, as they have not been applied to UVFP patients previously. Measuring parameters at baseline, after ML, and after AA in the same patient would be advantageous, allowing clinicians to determine the degree to which AA improves laryngeal function after ML. Testing other implant types and injection materials using the excised larynx setup may allow for a convenient determination of optimal treatment methods.

CONCLUSION
IL, ML, and ML-AA improved aerodynamic and acoustic phonatory parameters. High speed video recordings revealed significantly decreased amplitude of the mucosal wave after IL, preservation after ML, and even restoration of a normal mucosal wave after ML-AA. Though ML-AA produced the best results, improper rotation of the arytenoid in three larynges demonstrates the need to avoid hypo- and hyperadduction of the paralyzed fold during AA. The excised larynx setup used in this study represents a possible tool which could be used to develop new methods of treating vocal fold paralysis.

ACKNOWLEDGEMENTS

This study was funded by NIH grant numbers R01 DC008153, R01 DC05522, and R01 DC008850 from the National Institute on Deafness and other Communicative Disorders.

TABLES

Table I. Summary aerodynamic data presented as mean ± standard deviation (n=8). A significance level of \( \alpha = 0.05 \) was used for all tests. IL = injection laryngoplasty; ML = medialization laryngoplasty; ML-AA = medialization laryngoplasty with arytenoid adduction; PTF = phonation threshold flow (ml/s); PTP = phonation threshold pressure (cmH\(_2\)O); PTW = phonation threshold power (ml/s * cmH\(_2\)O). Significant p-values are denoted by an asterisk. P-values provided for ML-AA represent result of t-test comparing ML to ML-AA.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>IL Pre</th>
<th>IL Post</th>
<th>P-value</th>
<th>ML Pre</th>
<th>ML Post</th>
<th>P-value</th>
<th>ML-AA Post</th>
<th>ML-AA P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTF</td>
<td>109±88</td>
<td>55±37</td>
<td>0.007*</td>
<td>127±42</td>
<td>95±51</td>
<td>0.003*</td>
<td>50±26</td>
<td>0.008*</td>
</tr>
<tr>
<td>PTP</td>
<td>20.3±10.6</td>
<td>21.3±6.6</td>
<td>0.715</td>
<td>16.7±6.3</td>
<td>18.2±11.8</td>
<td>0.58</td>
<td>11.7±5.8</td>
<td>0.008*</td>
</tr>
<tr>
<td>PTW</td>
<td>2217±935</td>
<td>1179±247</td>
<td>0.097</td>
<td>2345±1571</td>
<td>2257±2375</td>
<td>0.818</td>
<td>713±750</td>
<td>0.008*</td>
</tr>
</tbody>
</table>

Table II. Summary of percent changes in aerodynamic parameters. Data are presented as mean ± standard deviation (n=8). A significance level of \( \alpha = 0.05 \) was used for all tests. Pre – IL = percent change from pre- to post-injection laryngoplasty; Pre – ML = percent change from pre-
to post-medialization laryngoplasty; P (IL, ML) = p-value comparing percent change of IL and ML; Pre – AA = percent change from baseline (simulated paralysis) to arytenoid adduction; P (IL, AA) = p-value comparing percent change of Pre – IL and Pre – AA; P (ML, AA) = p-value comparing percent change from pre- to post-ML and baseline to arytenoid adduction; PTF = phonation threshold flow; PTP = phonation threshold pressure; PTW = phonation threshold power.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pre – IL</th>
<th>Pre – ML</th>
<th>P (IL, ML)</th>
<th>Pre – AA</th>
<th>P (IL, AA)</th>
<th>P (ML, AA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTF</td>
<td>-31.8±25.0</td>
<td>-28.3±20.3</td>
<td>0.766</td>
<td>-60.9±13.3</td>
<td>0.028*</td>
<td>0.002*</td>
</tr>
<tr>
<td>PTP</td>
<td>-0.9±25.8</td>
<td>3.8±37.7</td>
<td>0.773</td>
<td>-29.1±23.1</td>
<td>0.038*</td>
<td>0.054</td>
</tr>
<tr>
<td>PTW</td>
<td>-29.4±37.9</td>
<td>-19.4±45.1</td>
<td>0.639</td>
<td>-69.8±18.9</td>
<td>0.017*</td>
<td>0.021*</td>
</tr>
</tbody>
</table>

Table III. Summary acoustic data presented as mean ± standard deviation (n=8). A significance level of α = 0.05 was used for all tests. IL = injection laryngoplasty; ML = medialization laryngoplasty; ML-AA = medialization laryngoplasty with arytenoid adduction; SNR = signal to noise ratio. Significant p-values are denoted by an asterisk. P-values provided for ML-AA represent result of t-test comparing ML to ML-AA.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>IL</th>
<th>ML</th>
<th>ML-AA</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Jitter</td>
<td>6.7±2.2</td>
<td>6.4±2.3</td>
<td>2.4±2.2</td>
</tr>
<tr>
<td>% Shimmer</td>
<td>24.3±8.5</td>
<td>25.9±10.2</td>
<td>16.1±16.8</td>
</tr>
<tr>
<td>SNR</td>
<td>3.5±1.7</td>
<td>4.2±4.3</td>
<td>11.5±8.5</td>
</tr>
<tr>
<td>Frequency (Hz)</td>
<td>300±287</td>
<td>210±57</td>
<td>138±30</td>
</tr>
</tbody>
</table>

Table IV. Summary of percent changes in acoustic parameters. Data are presented as mean ± standard deviation (n=8). A significance level of α = 0.05 was used for all tests. Pre – IL = percent change from pre- to post-injection laryngoplasty; Pre – ML = percent change from pre- to post-medialization laryngoplasty; P (IL, ML) = p-value comparing percent change of IL and ML; Pre – AA = percent change from baseline (simulated paralysis) to arytenoid adduction; P (IL, AA) = p-value comparing percent change of Pre – IL and Pre – AA; P (ML, AA) = p-value comparing percent change from pre- to post-ML and baseline to arytenoid adduction; SNR = signal to noise ratio.
Table V. Summary mucosal wave data presented as mean ± standard deviation (n=8). A significance level of α = 0.05 was used for all tests. IL = injection laryngoplasty; ML = medialization laryngoplasty; ML-AA = medialization laryngoplasty with arytenoid adduction. Amplitude and phase difference have arbitrary units. Glottal gap is measured in pixels. Significant p-values are denoted by an asterisk. P-values provided for ML-AA represent result of t-test comparing ML to ML-AA.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pre</th>
<th>Post</th>
<th>P-value</th>
<th>Pre</th>
<th>Post</th>
<th>P-value</th>
<th>Pre</th>
<th>Post</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amplitude</td>
<td>4.4±1.6</td>
<td>1.5±0.7</td>
<td>0.002*</td>
<td>3.0±1.3</td>
<td>3.1±1.7</td>
<td>0.879</td>
<td>5.4±4.0</td>
<td>0.128</td>
<td></td>
</tr>
<tr>
<td>Phase difference</td>
<td>-1.6±1.4</td>
<td>-0.4±0.9</td>
<td>0.042*</td>
<td>-0.3±1.8</td>
<td>-0.8±1.5</td>
<td>0.116</td>
<td>-0.2±1.1</td>
<td>0.342</td>
<td></td>
</tr>
<tr>
<td>Glottal gap</td>
<td>69.0±27.4</td>
<td>33.4±15.3</td>
<td>&lt;0.001*</td>
<td>66.3±18.0</td>
<td>42.9±18.9</td>
<td>&lt;0.001*</td>
<td>29.2±20.8</td>
<td>0.004*</td>
<td></td>
</tr>
</tbody>
</table>

Table VI. Summary of percent changes in mucosal wave parameters. Data are presented as mean ± standard deviation (n=8). A significance level of α = 0.05 was used for all tests. Pre – IL = percent change from pre- to post-injection laryngoplasty; Pre – ML = percent change from pre- to post-medialization laryngoplasty; P (IL, ML) = p-value comparing percent change of IL and ML; Pre – AA = percent change from baseline (simulated paralysis) to arytenoid adduction; P (IL, AA) = p-value comparing percent change of Pre – IL and Pre – AA; P (ML, AA) = p-value comparing percent change from pre- to post-ML and baseline to arytenoid adduction; SNR = signal to noise ratio.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pre – IL</th>
<th>Pre – ML</th>
<th>P (IL, ML)</th>
<th>Pre – AA</th>
<th>P (IL, AA)</th>
<th>P (ML, AA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amplitude</td>
<td>-60.4±25.6</td>
<td>13.9±59.9</td>
<td>0.006*</td>
<td>110.4±171.0</td>
<td>0.015*</td>
<td>0.092</td>
</tr>
<tr>
<td>Phase difference</td>
<td>-79.3±83.3</td>
<td>-19.0±99.9</td>
<td>0.05*</td>
<td>-165.5±261</td>
<td>0.328</td>
<td>0.008*</td>
</tr>
<tr>
<td>Glottal gap</td>
<td>-51.6±13.8</td>
<td>-37.1±12.8</td>
<td>0.047*</td>
<td>-59.4±18.0</td>
<td>0.346</td>
<td>0.007*</td>
</tr>
</tbody>
</table>

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CHAPTER 3

Multi-parameter analysis of titanium vocal fold medializing implant in an excised larynx model

Rachel E. Witt, Matthew R. Hoffman, Gerhard Friedrich, Adam L. Rieves, Benjamin J. Schoepke, and Jack J. Jiang

ABSTRACT

Objective: Evaluate the efficacy of the titanium vocal fold medializing implant (TVFMI) for the treatment of unilateral vocal fold paralysis (UVFP) based on acoustic, aerodynamic, and mucosal wave measurements in an excised larynx setup.

Methods: Measurements were recorded on eight excised canine larynges with simulated UVFP before and after medialization with the TVFMI.

Results: Phonation threshold flow (PTF) and phonation threshold power (PTW) decreased significantly after medialization (p<0.001; p=0.008). Phonation threshold pressure (PTP) also decreased, but this difference was not significant (p=0.081). Percent jitter and percent shimmer decreased significantly after medialization (p=0.005; p=0.034). Signal to noise ratio (SNR) increased significantly (p=0.05). Differences in mucosal wave characteristics were discernible, but not significant. Phase difference between the normal and paralyzed vocal fold and amplitude of the paralyzed vocal fold decreased (p=0.15; p=0.78). Glottal gap decreased significantly (p=0.004).

Conclusions: The TVFMI was effective in achieving vocal fold medialization, improving vocal aerodynamic and acoustic characteristics of phonation significantly and mucosal wave...
characteristics discernibly. This study provides objective, quantitative support for the use of the TVFMI in improving vocal function in patients with unilateral vocal fold paralysis.

INTRODUCTION

Unilateral vocal fold paralysis (UVFP) is typically caused by injury to the recurrent laryngeal nerve, which controls the intrinsic laryngeal muscles necessary for vocal fold adduction. The inability to adduct the paralyzed vocal fold impairs voice, swallowing, and breathing function (Havas 1999). Current treatment of glottic insufficiency due to unilateral VFP is primarily surgical, with the goal of medializing the paralyzed vocal fold to improve laryngeal function. Various autogenous and alloplastic materials have been utilized to adduct the paralyzed vocal fold and improve associated dysphonia. Vocal fold injections can be used to achieve vocal fold medialization by increasing volume and stiffness. Overcorrection of the vocal fold is difficult to reverse and negatively alters vocal fold configuration at the anterior commissure, leading to abnormal acoustic and aerodynamic parameters of phonation (Dedo 1992). Additionally, injected materials are reabsorbed by the surrounding tissue over time, which may decrease or negate the initial improvements in laryngeal function following surgery (Ellis 1987).

Since its introduction by Isshiki et al., thyroplasty has become an increasingly popular method for correcting unilateral VFP. This method entails medializing the vocal fold with an implant, commonly a silicone wedge, inserted through a window in the thyroid cartilage (Isshiki 1974; Isshiki 1975). Medialization thyroplasty has been found to improve vocal quality (LaBlance 1992; Sasaki 1990). Insertion of the implant is performed under local anesthesia which provides the ability to adjust the degree of medialization based on intraoperative
phonation (Koufman 1986). Thyroplasty also offers advantages over injection laryngoplasty. By inserting an implant, the membranous vocal fold structure is preserved and the procedure is reversible (Ford 1992). Injected material also tends to migrate through the laryngeal tissue over time, whereas solid implants maintain a stable shape and size (Remacle 1988).

Despite its benefits, thyroplasty with a silicone implant presents several disadvantages in both technique and implant material. The silicone implant must be carved during surgery, prolonging operation time and decreasing standardization. Suboptimal shaping can hinder success in improving breathing, swallowing, and voicing function (Koufman 1986; Cummings 1993; Montgomery 1997). Following the procedure, allergic reactions to silicone have also been observed (Hunsaker 1995). Submucosal hemorrhage and extrusion of the implant, causing obstruction of the laryngeal system, are also possible complications (Tucker 1993).

In response to the complications encountered in thyroplasty using a silicone implant, alternative implants have been proposed. These alternatives have included implants made of ceramic (Sakai 1996), Gore-Tex (McCulloch 1998), and hydroxylapatite (Cummings 1993). The concept of an adjustable implant has received attention recently because endolaryngeal swelling and hematoma can affect intraoperative evaluation of phonation when determining the degree of medialization. Adjustable implant systems, such as that developed by Montgomery et al., have attempted to standardize the shape and size of laryngeal implants to reduce trauma and time required for surgery. These implants also allow for postoperative adjustment without replacing the implant (Montgomery 1997; Desrosiers 1993). However, these adjustable implants had the disadvantage of complicated designs and discrete degrees of medialization. Previous adjustable
implants were composed of multiple parts and variation of medialization required manipulation of a monometric screw or the insertion of different sized preformed implants.

The titanium vocal fold medializing implant (TVFMI) was developed by Friedrich to address concerns regarding current thyroplasty techniques. The results of initial clinical trials indicated that the implant succeeded in significantly reducing the width of the glottal gap and had several advantages over previous methods of vocal fold medialization (Friedrich 1999). Using a preformed implant decreased operation time, which resulted in reduced intralaryngeal swelling and hematoma during and following surgery. The TVFMI is also unlikely to migrate through laryngeal tissue because it is compressed during insertion but expands to its original conformation in the laryngeal tissue, creating a secure fit with the thyroid window. Anchoring the implant with sutures to the thyroid lamina provides fixation and stabilization, further reducing the risk for extrusion. In a clinical study of 20 patients, no extrusion was observed 2, 6, or 12 months after the procedure. This system standardized implant shape and size, and the use of titanium provided the malleability necessary to adapt the implant to individual patients. In contrast to earlier adjustable implant models, the TVFMI provides adjustability in medialization along a continuous scale by pressing the posterior part of the implant inward and securing its dorsal flange to the thyroid cartilage to maintain that depth. The simplicity of the TVFMI allows for its adaptability by using standard otolaryngology equipment, similar to earlier thyroplasty methods, without the complication of forming an implant during surgery.

Additional studies have evaluated the effect of medialization thyroplasty using the TVFMI in patients with unilateral VFP. Videostroboscopy indicated almost complete glottal closure following thyroplasty in most patients (Schneider 2003). Subjective evaluations of
laryngeal function by patients indicated significant improvements in voice quality and vocal efficiency, as well as reduced hoarseness. There were also significant improvements in non-phonatory activities such as increased breathing control, reduced dyspnea during phonation, and recovered laughing and coughing capabilities. Acoustic analysis indicated significant decreases in percent jitter, percent shimmer, irregularity, and noise in the voice signal as well as significant increases in its period correlation and glottal-to-noise excitation ratio (Schneider 2003a; Schneider 2003b). Additionally, the TVFMI achieved vocal fold medialization without compromising respiratory performance. This was determined by observing the effect of medialization using the implant on pulmonary function during physical exertion (Schneider 2003c). Although previous studies have examined the effects of TVFMI on pulmonary function, its effects on aerodynamic parameters of phonation have not been examined.

The effect of TVFMI insertion on the mucosal wave has not been analyzed in patients or excised models. Although thyroplasty has been used as a technique for over twenty years, post-medialization mucosal wave has only been analyzed with stroboscopy and glottography (Tsuji 2003; McLean-Muse 2000; Thompson 1995; Slavit 1994). Videostroboscopy is unable to accurately image irregular patterns of vibration characterized by aperiodicity or changes in fundamental frequency because it creates a composite image of the mucosal wave averaged over several cycles (Bless 1987). High-speed video is an improved method of mucosal wave analysis because it allows for real-time visualization of the mucosal wave (Patel 2008). In comparing the accuracy of the two methods in characterizing the mucosal wave in pathological larynges, high-speed video was found to be significantly more accurate and interpretable than stroboscopy.
(Patel 2008; Bonilha 2008a; Bonilha 2008b). These attributes allow for quantification of the impact of TVFMI on vibration.

In this study, an excised larynx model was used to examine the effects of the TVFMI on the aerodynamic parameters of phonation threshold flow (PTF), phonation threshold pressure (PTP), and phonation threshold power (PTW), acoustic parameters of jitter, shimmer, and signal-to-noise ratio (SNR), and mucosal wave parameters of amplitude and phase difference. Previous studies have used excised canine larynges as a model for unilateral vocal fold paralysis. Noordzij et al. performed a series of studies evaluating arytenoid adduction and type I thyroplasty in a canine model (Noordzij 1998a; Noordzij 1998b; Noordzij 1998c). Additionally, the canine model has recently been used to model unilateral vocal fold paralysis by Czerwonka et al. (Czerwonka 2009). By taking measurements of these parameters in a controlled environment, the potential human variability that may be present in clinical studies was eliminated.

MATERIALS AND METHODS

Larynges

Eight larynges were harvested postmortem from canines sacrificed for non-research purposes. The larynges were excised according to the protocol described by Jiang and Titze (Jiang 1993). After excision, the larynges were examined for evidence of trauma or disorders and frozen in 0.9% saline solution.

Apparatus
Immediately prior to the experiment, the epiglottis, corniculate cartilages, cuneiform cartilages, and ventricular folds of each larynx were dissected away to expose the true vocal folds. The superior cornu and posterosuperior part of the thyroid cartilage ipsilateral to the normal vocal fold were also dissected away to facilitate insertion of lateral micrometers into the arytenoid cartilage. The larynx was mounted on the apparatus (Figure 1) as specified by Jiang and Titze (Jiang 1993). The trachea was fastened by a metal pull clamp to a tube connected to the pseudolung of the apparatus. Through the insertion of one 3-pronged micrometer in the arytenoid cartilage ipsilateral to the dissected thyroid cartilage (Figure 2A), only one vocal fold was adducted, simulating unilateral VFP with the unadducted vocal fold, as in Czerwonka et al. (Czerwonka 2009). The level of the adducted vocal fold was adjusted before the first trial by moving the micrometer in the superior and inferior directions until it was in the same plane as the unadducted vocal fold. The superior portion of the thyroid cartilage midline was sutured to a third micrometer, allowing for precise control of vocal fold elongation. The vocal fold adduction, height, and elongation remained constant by maintaining the same micrometer positions throughout trials.

The apparatus used to initiate and sustain phonation in these trials was designed to simulate the human respiratory system. Pressurized airflow was passed through two Concha Therm III humidifiers (Fisher & Paykel Healthcare Inc., Laguna Hills, California) in series to humidify and warm the air. The occurrence of dehydration was further diminished by frequent application of 0.9% saline solution between trials. Airflow was controlled manually throughout
the experiment and was measured by an Omega airflow meter (model FMA-1601A, Omega Engineering Inc., Stamford, Connecticut). Pressure measurements were taken immediately before the air passed into the larynx using a Heise digital pressure meter (901 series, Ashcroft Inc., Stratford, Connecticut).

Acoustic data were collected using a Sony microphone (model ECM-88, Sony Electronics Inc., New York, New York). The microphone was positioned at a 45° angle to the vertical axis of the vocal tract and approximately 10 cm from the glottis to minimize acoustic noise produced by turbulent airflow. The acoustic signal was subsequently amplified by a Symetrix preamplifier (model 302, Symetrix Inc., Mountlake Terrace, Washington). A National Instruments data acquisition board (model AT-MIO-16; National Instruments Corp, Austin, Texas) and customized LabVIEW 8.5 software were used to simultaneously record airflow, pressure, and acoustic data on a personal computer. Aerodynamic data were recorded at a sampling rate of 200 Hz and acoustic data were recorded at a sampling rate of 40,000 Hz. Experimental trials were conducted in a triple-walled, sound-proof room to reduce background noise and stabilize humidity levels and temperature.

The vocal fold mucosal wave was recorded for approximately 200 milliseconds during phonation by a high-speed digital camera (model Fastcam-ultima APX; Photron, San Diego, CA). High-speed videos of the movement were recorded with a resolution of 512 x 256 pixels at a rate of 4000 Hz.

**Experimental Methods**

Trials were conducted as a sequence of 5 second periods of phonation, followed by 5 second periods of rest. The sequence of phonating and resting periods was repeated on the same
larynx in succession for a total of ten cycles. During each period of phonation, airflow passing through the laryngeal system was manually increased gradually and consistently until the onset of phonation.

The TVFMI (Heinz Kurz Company, Dusslingen, Germany) was inserted into the larynx through a thyroplasty window in the thyroid cartilage ipsilateral to the paralyzed vocal fold according to the protocol described by Friedrich (Friedrich 1999). Optimal medialization was determined empirically by minimizing the aerodynamic power necessary to initiate phonation. This position was stabilized with sutures to the thyroid cartilage. The implant is available in three sizes, and different dimension thyroplasty windows are required for the insertion of each. In this study, the 13-mm implant was used in all larynges, requiring a 6 x 11 mm window.

Data Analysis

Phonation was evaluated before and after insertion of the implant. The measured values of airflow and pressure that coincided with the initiation of phonation were recorded as the onset phonation threshold flow (PTF) and onset phonation threshold pressure (PTP), respectively. Phonation threshold power (PTW) was calculated as the product of these values.

PTF, PTP, and PTW were determined manually with a custom LabVIEW 8.5 program. The program graphically displayed the spectrogram, airflow, and pressure signals as functions of time for each trial; airflow and pressure values corresponding to the initiation of phonation were recorded as PTF and PTP, respectively.

Acoustic analysis was done by measuring the signal-to-noise ratio (SNR) and the perturbation parameters of percent jitter and percent shimmer. The voice signal was trimmed
using the GoldWave 5.1.2600.0 program (GoldWave Inc., St. John’s, Canada), and acoustic analysis was conducted using Computerized Speech Lab (CSpeech) software (Madison, WI).

High speed video recordings of the mucosal wave were analyzed using a customized MATLAB program (The MathWorks, Natick, MA). The vibratory properties of each of the four vocal fold lips (right-upper, right-lower, left-upper, left-lower) were quantified via digital videokymography (VKG), a line-scan imaging technique. Threshold-based edge detection, manual wave segment extraction, and non-linear least squares curve fitting using the Fourier Series equation were applied to the VKG to determine the most closely fitting sinusoidal curve. The coefficients of the wave function for this curve were used to derive the frequency, amplitude, and phase of the mucosal wave of each vocal fold lip, both before and after implant insertion. Inter-vocal fold phase difference was calculated as the absolute value of the divergence between the sinusoidal phase measurements for the right and left upper folds. Mucosal wave amplitude was calculated as the average of the amplitudes of the upper and lower paralyzed vocal fold lips. Using the available technology, only relative values rather than absolute values could be obtained. This was sufficient for pre-/post-treatment comparisons. Changes in glottal gap were evaluated by measuring the relative change after medialization.

Paired t-tests were used to determine if inserting the implant had a significant effect on the measured parameters. If data were not

![Figure 3. Effect of TVFMI insertion on PTW.](image)
normal, a Mann-Whitney Rank Sum Test was performed. Tests were two-tailed and a significance level of $\alpha=0.05$ was used.

RESULTS

Paired $t$-tests demonstrated that there were significant decreases in PTF and PTW after medialization. PTF decreased from 127 mL/s to 46 mL/s ($p<0.001$) and PTW decreased from 2301 mL/s*cmH$_2$O to 649 mL/s*cmH$_2$O ($p=0.008$) (Figure 3). PTP decreased from 16.41 cmH$_2$O to 12.48 cmH$_2$O after medialization, but this difference was not significant ($p=0.081$).

There were significant changes in SNR, percent jitter, and percent shimmer after medialization. Mean SNR increased from 2.43 to 6.65 ($p=0.05$). Percent jitter decreased from 7.15% to 3.58% and percent shimmer decreased from 27.80% to 13.69% ($p=0.005$; $p=0.034$).

There was also a significant decrease in glottal gap. Glottal gap decreased from 68.98 to 30.75 ($p=0.004$) (Figure 4). Although differences in phase difference and amplitude of the mucosal wave were discernible, they were not significant. Mean phase difference between the normal and paralyzed vocal folds decreased from 1.03 to 0.008 ($p=0.15$). Mean amplitude of the paralyzed vocal fold decreased from 1.71 to 1.64 ($p=0.78$).

Summary data are presented in table 1.

DISCUSSION
This study provides an objective evaluation of the effect of TVFMI insertion on the aerodynamic, acoustic, and mucosal wave characteristics of phonation. By simulating UVFP in an excised larynx model, these measurements were taken in a controlled and repeatable environment. The results supplement those of previous studies that have examined the effect of the implant on pulmonary aerodynamic and acoustic characteristics of phonation and provide support for its therapeutic use in the treatment of UVFP.

Inserting the TVFMI decreased the aerodynamic power necessary to produce phonation. This was caused by medialization of the paralyzed vocal fold as demonstrated by a significant reduction in glottal gap. The decrease in PTF was significant, whereas the decrease PTP was not. This may be because PTF is more sensitive than PTP to changes in glottal abduction as demonstrated in an excised larynx experiment by Hottinger et al. (Hottinger 2007).

This decrease in the airflow required to initiate phonation also increases the acoustic quality of the voice signal. SNR increased because signal power in the form of phonation increased while noise power in the form of airflow decreased. Additionally, decreases in the perturbation measures of percent jitter and percent shimmer were also observed and can be attributed to vocal fold medialization restoring vocal fold contact and vibrational periodicity.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pre-TVFMI</th>
<th>Post-TVFMI</th>
<th>Percent change</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTF</td>
<td>127 ± 43</td>
<td>46 ± 27</td>
<td>-63</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>PTP</td>
<td>16.4 ± 7.13</td>
<td>12.48 ± 6.47</td>
<td>-24</td>
<td>0.081</td>
</tr>
<tr>
<td>PTW</td>
<td>2301 ± 1698</td>
<td>649 ± 644</td>
<td>-72</td>
<td>0.008*</td>
</tr>
<tr>
<td>SNR</td>
<td>2.43 ± 1.19</td>
<td>6.65 ± 4.55</td>
<td>174</td>
<td>0.03*</td>
</tr>
<tr>
<td>Percent jitter</td>
<td>7.15 ± 1.78</td>
<td>3.58 ± 1.96</td>
<td>-50</td>
<td>0.005*</td>
</tr>
<tr>
<td>Percent shimmer</td>
<td>27.80 ± 9.00</td>
<td>13.69 ± 11.07</td>
<td>-51</td>
<td>0.034*</td>
</tr>
<tr>
<td>Phase difference</td>
<td>1.03 ± 0.70</td>
<td>0.008 ± 1.49</td>
<td>-99</td>
<td>0.15</td>
</tr>
<tr>
<td>Glottal gap</td>
<td>68.98 ± 27.21</td>
<td>30.75 ± 6.04</td>
<td>-55</td>
<td>0.004*</td>
</tr>
<tr>
<td>Amplitude</td>
<td>1.71 ± 1.05</td>
<td>1.64 ± 0.73</td>
<td>-4</td>
<td>0.78</td>
</tr>
</tbody>
</table>

Table 1. Summary statistics before and after titanium vocal fold medializing implant (TVFMI) insertion. PTF=phonation threshold flow; PTP=phonation threshold pressure; PTW=phonation threshold power; SNR=spectral-to-noise ratio. Asterisk denotes significant p-value.
There were discernible changes in the mucosal wave characteristics following TVFMI insertion, though these differences were not significant. Thyroplasty type I increases the closed phase over one cycle, improving glottic vibration which has been correlated with more efficient phonation (Omori 2000). The study of hemilaryngeal phonation performed by Jiang and Titze indicated that a surface is required for proper vibration and phonation (Jiang 1993). Simulated paralysis causes abnormal vibration because neither fold has a surface against which it can vibrate; adducting the paralyzed fold restores vibrational harmony. The decrease in inter-vocal fold phase difference after medialization suggests that medialization increased synchronization of the mucosal waves.

The lack of significance in this decrease may have resulted from an insufficient sample size. It could also be due to inadequate color contrast in some of the video recordings. Analysis is dependent on threshold-based edge detection and the subsequent fitting of a sinusoidal curve to the mucosal wave. Threshold-based edge detection requires color contrast between the vocal fold tissue and the glottal gap. Although mucosal wave movement was still discernible on the paralyzed vocal fold following TVFMI insertion, the adduction of the vocal fold by the implant made this contrast difficult to distinguish.

Hyper-adduction of the vocal fold would result in increased jitter and shimmer; the results of this study indicate that hyper-adduction did not occur, as jitter and shimmer were both significantly decreased. Hyper-adduction would also lead to pressed phonation due to complete closure of the glottic gap; however, the glottic gap was significantly decreased but not eliminated.
Although the TVFMI is a patented implant for clinical use, the measurement of acoustic, aerodynamic, and mucosal wave parameters in a controlled setting provides additional support for its use. Physicians in different regions have personal preferences for the numerous materials used in thyroplasty; standardized measurements of the effects of different implants provide a quantitative basis for their comparison. The TVFMI is not yet widely used in the United States, so additional information on its effectiveness in treating unilateral vocal fold paralysis may benefit clinicians. This study further contributes to the body of scientific research because it examined the effects of medialization using TVFMI on physiological parameters, including the novel parameters of phonatory aerodynamics and high-speed video analysis of mucosal wave.

The results of this study provide objective support for the TVFMI that supplements previous human subject studies (Schneider 2003a; Schneider 2003b; Schneider 2003c). By examining the effect of the procedure on a comprehensive range of phonatory parameters in a controlled experimental setting, variation in these parameters unrelated to TVFMI insertion was reduced. Although Schneider et al. determined that TVFMI insertion did not affect aerodynamic parameters relating to pulmonary function during physical exertion, the effect of this procedure on vocal aerodynamics has not been previously studied (Schneider 2003b; Schneider 2003c).

Future research could use the excised larynx model to compare TVFMI insertion to injection or thyroplasty using other materials such as Silastic or hydroxylapatite. This would allow for objective assessment and direct quantitative comparisons between different treatments for UVFP.
This is the first study evaluating the effect of TVFMI insertion on vocal aerodynamics and mucosal wave characteristics. Future studies could measure these parameters in human subjects with the aim of quantitatively determining optimal implant position.

CONCLUSION

The TVFMI was effective in achieving vocal fold medialization, significantly improving vocal aerodynamic and acoustic characteristics of phonation and discernibly improving mucosal wave characteristics. This study provides objective, quantitative support for the use of the TVFMI in improving vocal function in patients with unilateral vocal fold paralysis.

ACKNOWLEDGEMENTS

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CHAPTER 4
Optimal arytenoid adduction based on quantitative real-time voice analysis
Matthew R. Hoffman, Ketan Surender, William J. Chapin, Rachel E. Witt, Timothy M. McCulloch, and Jack J. Jiang

ABSTRACT

**Hypothesis:** The optimal degree of arytenoid rotation for arytenoid adduction (AA) can be determined using quantitative real-time voice analysis.

**Study design:** Repeated measures with each larynx serving as its own control.

**Methods:** Unilateral vocal fold paralysis (VFP) was modeled in five excised canine larynges. Medialization laryngoplasty (ML) was performed, followed by AA. The optimal degree of arytenoid rotation was determined using real-time measurements of vocal efficiency ($V_E$), percent jitter, and percent shimmer. After the optimal degree of rotation was determined, the arytenoid was hypo- and hyper-rotated $10\pm2\%$ of the optimal angle to mimic hypoadducted and hyperadducted states. Aerodynamic, acoustic, and mucosal wave measurements were recorded.

**Results:** Mean optimal angle of arytenoid adduction was $151.4 \pm 2.5^\circ$. $V_E$ differed significantly across experimental conditions ($p = 0.003$). Optimal AA produced the highest $V_E$ of any treatment, but this value did not reach that produced in the normal condition. Percent jitter ($p < 0.001$) and percent shimmer ($p < 0.001$) differed across groups and were lowest for optimal AA. Mucosal wave amplitude of the normal ($p = 0.001$) and paralyzed fold ($p = 0.043$) differed across treatments. Amplitude of both folds was highest for optimal AA.

**Conclusions:** $V_E$ and perturbation parameters were sensitive to the degree of arytenoid rotation. Using real-time voice analysis may aid surgeons in determining the optimal degree of arytenoid
rotation when performing AA. Testing this method in patients and determining if optimal vocal outcomes are associated with optimal respiratory and swallowing outcomes will be essential to establishing clinical viability.

INTRODUCTION

Arytenoid adduction (AA) was introduced by Isshiki et al. as an additional treatment for vocal fold paralysis (VFP), primarily indicated for patients with a wide glottal chink or bilateral superoinferior vocal fold asymmetry (Isshiki 1978). Sutures passed from the muscular process of the arytenoid through the thyroid cartilage can simulate the contractile forces of the lateral cricoarytenoid and thyroarytenoid muscles, medializing a paralyzed fold when tension is placed on the suture. Due to the cylindrical shape of the cricoarytenoid joint (Isshiki 1978), the vocal process moves downward during adduction and can correct a difference in the levels of the vocal folds by lowering the affected fold (Neuman 1994).

Though the procedure has shown great utility and can effectively decrease a wide posterior glottal gap, surgical success of the procedure is inconsistent (Inagi 2002). Determination of optimal adduction is based on empirical judgments made during intraoperative voicing, a subjective and potentially time-consuming method which does not consistently yield optimal results (Inagi 2002). Locating and manipulating the muscular process is also difficult, giving the procedure a high level of technical difficulty (Slavit 1992) and decreasing the frequency with which it is performed.

When performed correctly, AA can produce dramatic improvement in laryngeal function. In a study retrospectively comparing patients undergoing medialization laryngoplasty (ML) and
simultaneous ML-AA, patients undergoing ML-AA had significantly better vocal improvement as evaluated by the GRBAS rating scale and patient satisfaction (McCulloch 2000). ML is limited by an inability to close a wide posterior glottal chink and correct a difference in the horizontal plane of the vocal folds. This is due to the posterior glottis and arytenoids residing outside the paraglottic space affected by the thyroplasty implant (McCulloch 2000).

One of the more common complications reported from AA is airway compromise (Kraus 1999; Rosen 1998). This can be attributed to overrotation of the arytenoid and consequent hyperadduction of the vocal fold beyond the glottal midline. Such hyperadduction compromises vocal outcomes as well, resulting in a pressed vocal quality. Dysphagia has also been reported following AA (Mortensen 2009), possibly due to hypoadduction and consequent residual glottis insufficiency. Due to the increased morbidity associated with AA, some authors question whether the procedure is warranted (Morgan 2007); however, the added improvement of AA after ML provides support for its use (Hoffman 2010). Developing an objective, quantitative evaluation may allow surgeons to more efficiently and accurately evaluate the degree of adduction, maximizing procedural benefit and reducing risk. We employed real-time measures of percent jitter, percent shimmer, and vocal efficiency ($V_E$) to determine the optimal degree of arytenoid rotation in an excised larynx setup. We also examined mucosal wave characteristics to determine if this optimal degree of rotation produced the greatest improvement in vocal fold vibration.

**MATERIALS AND METHODS**

*Larynges*
Five larynges were excised postmortem from canines sacrificed for non-research purposes according to the protocol described by Jiang and Titze (Jiang 1993). As the size and histological properties of the canine and human larynx are similar (Noordzij 1998), it is an appropriate model for studying human laryngeal physiology. Larynges were examined for evidence of trauma or disorders; any larynges exhibiting trauma or disorders were excluded. Following visual inspection, larynges were frozen in 0.9% saline solution.

**Apparatus**

Prior to the experiment, the epiglottis, corniculate cartilages, cuneiform cartilages, and ventricular folds were dissected away to expose the true vocal folds. The superior cornu and posterosuperior part of the thyroid cartilage ipsilateral to the normal vocal fold were also dissected away to facilitate insertion of a lateral 3-pronged micrometer into the arytenoid cartilage. The larynx was mounted on the apparatus (figure 1) as specified by Jiang and Titze (Jiang 1993). A metal pull clamp was used to stabilize the trachea to a tube connected to a pseudolung which served as a constant pressure source. Insertion of one 3-pronged micrometer in the arytenoid cartilage ipsilateral to the dissected thyroid cartilage allowed for adduction of one vocal fold, simulating UVFP in the unadducted vocal fold as in Czerwonka et al. (Czerwonka 2009), Witt et al. (Witt 2010), and Hoffman et al. (Hoffman 2010). An additional 3-pronged micrometer was placed against the contralateral thyroid lamina for stability without providing vocal fold adduction. Methodological consistency was maintained by always adducting the contralateral arytenoid (simulated normal) to the
midline. Micrometer positioning remained constant across sets of trials within the same larynx. Tension on the vocal folds and control of vocal fold elongation was accomplished by attaching the superior anteromedial thyroid cartilage, just inferior to the thyroid notch, to an anterior micrometer. Vocal fold elongation and adduction remained constant for all trials.

The pseudolung used to initiate and sustain phonation in these trials was designed to simulate the human respiratory system. Pressurized airflow was passed through two Concha Therm III humidifiers (Fisher & Paykel Healthcare Inc., Laguna Hills, California) in series to humidify and warm the air. The potential for dehydration was further decreased by frequent application of 0.9% saline solution between trials. Airflow was controlled manually and was measured using an Omega airflow meter (model FMA-1601A, Omega Engineering Inc., Stamford, Connecticut). Pressure measurements were taken immediately before the air passed into the larynx using a Heise digital pressure meter (901 series, Ashcroft Inc., Stratford, Connecticut).

Acoustic data were collected using a dbx microphone (model RTA-M, dbx Professional Products, Sandy, Utah) positioned at a 45° angle to the vocal folds. The microphone was placed 10 cm from the glottis to minimize acoustic noise produced by turbulent airflow. Acoustic signals were subsequently amplified by a Symetrix preamplifier (model 302, Symetrix Inc., Mountlake Terrace, Washington). A National Instruments data acquisition board (model AT-MIO-16; National Instruments Corp, Austin, Texas) and customized LabVIEW 8.5 software were used to record airflow, pressure, and acoustic signals on a personal computer. Aerodynamic data were recorded at a sampling rate of 100 Hz and acoustic data at 40,000 Hz. Experiments
were conducted in a triple-walled, sound-proof room to reduce background noise and stabilize humidity levels and temperature.

The vocal fold mucosal wave was recorded for approximately 200 milliseconds per trial using a high-speed digital camera (model Fastcam-ultima APX; Photron, San Diego, CA). Videos were recorded with a resolution of 512 x 256 pixels at a rate of 4000 Hz.

**Experimental Methods**

Trials were conducted as a sequence of 5 second periods of phonation, followed by 5 second periods of rest. Five trials were performed for each condition. During each trial, airflow passing through the larynx was increased gradually and consistently until the onset of phonation. All procedures were performed by the same author (MRH) under the supervision of the senior author (TMM). Larynges were thoroughly hydrated with saline solution between trials and between sets of trials to eliminate any potentially confounding effects of dehydration.

ML was performed using a Silastic implant (Dow Corning Corporation, Midland, MI). The implant was inserted through a 6 x 11 mm thyroplasty window in the thyroid cartilage ipsilateral to the paralyzed vocal fold. AA was performed after a set of trials was conducted analyzing the effect of ML. The procedure was performed according to the clinical descriptions by Isshiki (Isshiki 1978). One suture was passed with a needle from the muscular process of the
arytenoid anteriorly through the paraglottic space through the thyroid cartilage just lateral to the anterior commissure and the second inferior to the cartilage was tightened to rotate the arytenoid and adduct the simulated paralyzed fold. The optimal degree of rotation was determined using real-time measurements of $V_E$ primarily and percent jitter and percent shimmer secondarily. After trials were performed at the optimal degree of rotation, the arytenoid was hypo- and hyper-rotated 10±2% of the optimal angle created by the glottal axis and medial aspect of the arytenoid ipsilateral to the simulated paralyzed fold (figure 2).

Data Analysis

Airflow and pressure at the phonation onset were recorded as the phonation threshold flow (PTF) and phonation threshold pressure (PTP), respectively. Phonation threshold power (PTW) was calculated as the product of these values. PTF, PTP, and PTW were determined manually using customized LabVIEW 8.5 software.

Measured acoustic parameters included frequency, signal-to-noise ratio (SNR), percent jitter, and percent shimmer. Acoustic signals were trimmed using GoldWave 5.1.2600.0 (GoldWave Inc., St. John’s, Canada) and analyzed using TF32 software (Madison, WI).

High speed video recordings of the mucosal wave were analyzed using a customized MATLAB program (The MathWorks, Natick, MA). Vibratory properties of each of the four vocal fold lips (right-upper, right-lower, left-upper, left-lower) were quantified via digital videokymography (VKG). Threshold-based edge detection, manual wave segment extraction, and non-linear least squares curve fitting using the Fourier Series equation were applied to determine the most closely fitting sinusoidal curve. This curve was used to derive the amplitude and phase difference of the mucosal wave of each vocal fold lip, both before and after treatment.
Interfold phase difference was calculated as the phase difference between the right upper and left upper vocal fold lips while intrafold phase difference was calculated as the phase difference between the upper and lower lips of the right (paralyzed) vocal fold. Mucosal wave amplitude was calculated as the average of the amplitudes of the upper and lower paralyzed vocal fold lips. While only relative rather than absolute values could be obtained due to current technological limitations, this was sufficient for the treatment comparisons performed in this study.

**Statistical analysis**

One-way repeated measures analysis of variance (ANOVA) was performed to determine if parameters changed across the six experimental conditions (normal, paralyzed, ML, hypoadducted AA, optimal AA, and hyperadducted AA). If data were not normal according to a Shapiro-Wilk test or did not display equal variance according to a Levene’s test, ANOVA on ranks was performed. Paired t-tests were performed on each possible condition pairing to further analyze potential differences in each parameter measured. If data did not meet assumptions for parametric testing, a Wilcoxon-Mann-Whitney rank sum test was used. Tests were two-tailed and a significance level of $\alpha=0.05$ was used for all statistical tests.

**RESULTS**

*Optimal angle of arytenoid adduction*
Mean optimal angle of arytenoid adduction was $151.4 \pm 2.5^\circ$. The arytenoid was then hypo- and hyper-rotated to mean angles of $161.6 \pm 11.2^\circ$ and $143.4 \pm 13.5^\circ$, respectively.

Summary aerodynamic, acoustic, and mucosal wave data are presented in tables I, II, and III. Results from paired $t$-tests are provided in table IV.

**Aerodynamics**

PTF ($p < 0.001$) and PTW ($p = 0.011$) differed significantly across treatment groups, while PTP did not ($p = 0.193$). PTF, PTP, and PTW were lowest for the optimal AA treatment. $V_E$ also differed significantly across treatments ($p = 0.003$). Optimal AA produced the highest $V_E$ of any treatment, and was insignificantly less than for normal (figure 3) ($p = 0.625$). The differences in $V_E$ relative to the other treatments approached, but did not reach significance (table IV).

**Acoustics**

Percent jitter ($p < 0.001$), percent shimmer ($p < 0.001$), and SNR ($p < 0.001$) differed significantly across treatment groups. Percent jitter and percent shimmer for optimal AA were the lowest for any treatment (figures 4, 5). Perturbation was significantly lower for optimal AA.
compared to ML, and discernibly lower compared to hypo- and hyperadducted AA (table IV). The percent shimmer for optimal AA was also lower than that for the normal condition, though this difference was not significant. Frequency differed significantly across treatment groups (p = 0.017) and was highest for the normal condition. SNR was highest for the normal condition, but this was not significantly greater than the SNR produced by any of the AA conditions (table IV).

*Mucosal wave*

Amplitude of the normal fold (p = 0.001) and paralyzed fold (p = 0.043) differed significantly across treatment groups. No significant changes occurred for intrafold (p = 0.303) or interfold phase difference (p = 0.973). Amplitude of both the left (simulated normal) and right (simulated paralyzed) folds decreased significantly upon simulating the paralyzed condition. Optimal AA produced the greatest amplitude for both folds (figure 6).

**DISCUSSION**

We present a quantitative method for determining the optimal degree of arytenoid rotation when performing AA using real-time voice measurements. This is a preliminary study establishing the validity of this method and the sensitivity of the chosen measures to small changes in arytenoid position. Ex vivo canine larynges have been used extensively to study vocal
fold paralysis (Hoffman 2010; Noordzij 1998; Czerwonka 2009; Witt 2010). There are several anatomical differences in the canine larynx relative to the human, including more angulated thyroid and cricoid cartilages, and the absence of a well-defined vocal ligament (Noordzij 1998). These differences did not affect the procedures performed in this study.

This is our second study examining the added benefit of performing AA after ML in excised canine larynges (Hoffman 2010). By optimizing the degree of arytenoid rotation, we observed even greater changes in all parameters of interest. While assessing the added benefit of AA following ML in patients can be difficult as the two procedures are often performed simultaneously, this can easily be done using the excised larynx setup. Our results provide additional support for the use of AA in patients who can tolerate it.

Aerodynamic parameters behaved as expected, with increases in PTF and PTP occurring in the simulated paralysis condition, and stepwise decreases occurring from paralysis to ML to AA. As observed previously (Hoffman 2010; Witt 2010), PTF varied significantly across treatments while PTP did not. PTF is directly related to the cube of neutral glottal half-width\(^{15}\) and is more sensitive than PTP to changes in glottal abduction (Hottinger 2007). While the threshold parameters displayed differences across the three AA conditions, the differences were not as evident as for perturbation parameters or \(V_E\). Accurate measurement of threshold aerodynamics, particularly PTF, also remains a challenge. PTP and PTF, therefore, are likely not suitable parameters for intraoperative voice assessment.

Perturbation parameters, however, may offer a more reliable and feasible alternative for determining optimal arytenoid rotation. Recording requires only a microphone and software equipped with the real-time measurement employed in this study. Percent jitter and percent
shimmer were both sensitive to arytenoid position, with the optimal AA angle producing the lowest values. Fundamental frequency was significantly lower for the AA conditions relative to normal, but this may be a result of the experimental design. Phonation tokens were recorded at the phonation threshold. As PTP was lowest in the AA conditions and pressure has a direct relationship with frequency, fundamental frequency was lower. A decrease in $F_0$ following AA has also been reported previously (Su 2002). Increases in SNR can be attributed to decreased flow (noise) as well as increased sound production (signal), with optimal AA producing the most dramatic improvement. Real-time intraoperative measurements of SNR may not be beneficial though, as an extremely hyperadducted larynx would have a high SNR due to minimal flow escaping the glottis.

Changes in mucosal wave amplitude were of particular interest, as dramatic changes occurred across the three AA conditions for both folds (table III). Real-time mucosal wave analysis is currently not feasible due to the laborious nature of extracting parameters from a segment of high speed video. As extraction and analysis techniques are improved, real-time mucosal wave amplitude analysis may offer another means of determining the optimal degree of arytenoid rotation. Intrafold phase difference reflects the presence or absence of a normal mucosal wave. Ideally, there should be a phase difference of pi between the upper and lower lips of the vocal fold. A phase difference similar to this was observed in both the normal and optimal AA conditions. Thus, the optimal degree of arytenoid rotation produced the greatest improvements in vocal fold vibratory characteristics. Intrafold phase difference was decreased in the other conditions. There did not appear to be a pattern for change in interfold phase difference across conditions.
Differences in $V_E$ and perturbation parameters across the three AA conditions were not significant; however, significant differences were not expected for the subtle changes in arytenoid position that were analyzed. The primary objective of this study was to demonstrate that $V_E$ and perturbation parameters were sensitive to changes in arytenoid rotation, increasing and decreasing, respectively, until the optimal degree of rotation was reached. As the differences did approach significance, particularly for $V_E$, one could anticipate that significant differences may be found with a larger sample size.

$V_E$ was used with success in this study to distinguish among subtle differences in arytenoid rotation when performing AA. It may be potentially more useful than perturbation parameters as it evaluates both aerodynamics, the input to voice production, and acoustics, the output. For several other measured parameters such as percent jitter and threshold aerodynamics, hyperadducted AA performed rather similarly to optimal AA. However, there was over a four-fold increase in $V_E$ for optimal AA compared to hyperadducted AA (table I, figure 3). As hyperadduction can lead to postoperative dyspnea, it is important to measure parameters which vary significantly with subtle changes in arytenoid rotation. $V_E$, therefore, may represent the most useful parameter for determining the optimal degree of arytenoid rotation during AA.

Both $V_E$ and perturbation parameters can be measured intraoperatively. Measuring perturbation parameters would be easier, as it would require only a microphone and the software used in this study. Measurement of $V_E$ could be done using the airflow interrupter (Jiang 1999), which uses a mechanical balloon valve to interrupt sustained phonation. Airflow interruption has been used with success to assess disordered subjects (Jiang 2004) and could be applied to patients with VFP. This method would require more patient cooperation than measurement of
perturbation parameters. Alternatively, aerodynamic measures could be obtained directly via a cricothyroid membrane puncture. This, coupled with acoustic measurements obtained with a microphone, could also be used to measure $V_E$. Patients would then need only to produce a sustained vowel for all measurements to be recorded. Evaluating both $V_E$ and perturbation parameters clinically would be valuable to determine which can adequately distinguish among different degrees of arytenoid rotation while minimizing demands on patient vocal effort. The degree to which the implementation of each increases operative time must also be analyzed. Intraoperative edema resultant from increased operative time may confound measurement and lead to an arytenoid position which is not optimal. Real-time voice analysis also has the ability to reduce intraoperative edema, as it eliminates potentially time-consuming subjective voice assessment. A surgeon can rotate the arytenoid along an arc until $V_E$ stops increasing and perturbation measures stop decreasing. This point would not be found as easily if using subjective voice assessment.

It is also important to evaluate the use of real-time voice measurements in patients to determine if optimal vocal outcomes are associated with optimal respiratory and swallowing outcomes. AA has been associated with improvement in voice, swallowing, and respiratory function (Kraus 1999); however, examining swallowing and respiratory function after performing AA with real-time voice measurements is necessary if this method is to be applied clinically. One limitation of the excised larynx setup is that only vocal function can be analyzed. The angle we found to be optimal may be slightly more acute than what would be optimal for the larynx of a human patient. Though the paralyzed vocal fold was adducted just past the midline (figure 2b), this degree of adduction may be sufficient to cause episodic dyspnea. This concern
must be considered when utilizing intraoperative voice analysis. Future investigations will focus on balancing the desire for a good vocal outcome with the need for a good respiratory outcome.

CONCLUSION

Real-time measurements of vocal efficiency and perturbation parameters are proposed to guide surgeons when performing arytenoid adduction. Testing in an excised larynx setup demonstrated that these measurements are sensitive to the degree of arytenoid rotation. Rotating the arytenoid until vocal efficiency stops increasing and perturbation parameters stop decreasing may yield the optimal arytenoid position for voice production. Determining if optimal vocal outcomes are associated with optimal respiratory and swallowing outcomes will be essential to establishing the clinical viability of this method.

ACKNOWLEDGEMENTS

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TABLES

Table I. Summary aerodynamic data presented as mean ± standard deviation (n=5). A significance level of \( \alpha=0.05 \) was used for all tests. PTF = phonation threshold flow (ml/s); PTP = phonation threshold pressure (cmH\(_2\)O); PTW = phonation threshold power (ml/s * cmH\(_2\)O); \( \text{V}_{\text{E}} \) = vocal efficiency (units); VFP = vocal fold paralysis; ML = medialization laryngoplasty; hypo AA = hypoadducted arytenoid adduction; optimal AA = optimally adducted arytenoid adduction; hyper AA = hyperadducted arytenoid adduction. Values are presented as median (interquartile range).
### Table II. Summary acoustic data presented as mean ± standard deviation (n=5). A significance level of α = 0.05 was used for all tests. SNR = signal-to-noise ratio; $F_0$ = fundamental frequency; VFP = vocal fold paralysis; ML = medialization laryngoplasty; hypo AA = hypoadducted arytenoid adduction; optimal AA = optimally adducted arytenoid adduction; hyper AA = hyperadducted arytenoid adduction. Values are presented as median (interquartile range).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal</th>
<th>VFP</th>
<th>ML</th>
<th>Hypo AA</th>
<th>Optimal AA</th>
<th>Hyper AA</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Jitter</td>
<td>0.762 (1.33)</td>
<td>5.09 (3.62)</td>
<td>4.24 (1.43)</td>
<td>2.27 (2.67)</td>
<td>0.815 (1.48)</td>
<td>1.10 (5.33)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>% Shimmer</td>
<td>3.96 (3.41)</td>
<td>28.8 (12.7)</td>
<td>32.2 (19.3)</td>
<td>9.95 (13.9)</td>
<td>4.85 (3.25)</td>
<td>4.23 (5.18)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SNR</td>
<td>16.1 (8.0)</td>
<td>11.5 (7.7)</td>
<td>4.09 (4.8)</td>
<td>23.7 (22.9)</td>
<td>22.7 (15.7)</td>
<td>19.3 (16.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>$F_0$ (Hz)</td>
<td>215 (117)</td>
<td>174 (58)</td>
<td>237 (168)</td>
<td>159 (177)</td>
<td>149 (75)</td>
<td>169 (75)</td>
<td>0.017</td>
</tr>
</tbody>
</table>

### Table III. Summary mucosal wave data presented as mean ± standard deviation (n=8). A significance level of α = 0.05 was used for all tests. Amplitude (L) = amplitude of left vocal fold (simulated normal); amplitude (R) = amplitude of right vocal fold (simulated paralyzed); intrafold $\Delta \Phi$ = phase difference between upper and lower lips of right vocal fold; interfold $\Delta \Phi$ = phase difference between upper lips of left and right folds; VFP = vocal fold paralysis; ML = medialization laryngoplasty; hypo AA = hypoadducted arytenoid adduction; optimal AA = optimally adducted arytenoid adduction; hyper AA = hyperadducted arytenoid adduction. Amplitude and phase difference have arbitrary units. Values are presented as median (interquartile range).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal</th>
<th>VFP</th>
<th>ML</th>
<th>Hypo AA</th>
<th>Optimal AA</th>
<th>Hyper AA</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amplitude (L)</td>
<td>8.41 (8.25)</td>
<td>3.39 (1.71)</td>
<td>1.35 (2.52)</td>
<td>2.52 (2.47)</td>
<td>8.21 (4.83)</td>
<td>5.78 (7.52)</td>
<td>0.001</td>
</tr>
<tr>
<td>Amplitude (R)</td>
<td>7.48 (5.27)</td>
<td>4.99 (2.63)</td>
<td>3.51 (2.33)</td>
<td>4.50 (2.49)</td>
<td>8.42 (7.19)</td>
<td>7.18 (5.20)</td>
<td>0.043</td>
</tr>
<tr>
<td>Intrafold $\Delta \Phi$</td>
<td>3.20 (5.20)</td>
<td>-0.044 (5.09)</td>
<td>-0.224 (4.97)</td>
<td>-0.311 (5.57)</td>
<td>0.424 (7.62)</td>
<td>0.475 (1.20)</td>
<td>0.303</td>
</tr>
<tr>
<td>Interfold $\Delta \Phi$</td>
<td>-0.603 (4.31)</td>
<td>0.228 (2.45)</td>
<td>0.405 (3.73)</td>
<td>0.816 (3.11)</td>
<td>0.761 (2.21)</td>
<td>0.043 (6.38)</td>
<td>0.973</td>
</tr>
</tbody>
</table>
Table IV. P-values from paired t-tests comparing acoustic, aerodynamic, and mucosal wave parameters for all possible condition pairings. SNR = signal-to-noise ratio, PTF = phonation threshold flow, PTP = phonation threshold pressure, VE = vocal efficiency, Amplitude R = amplitude of right vocal fold, Amplitude L = amplitude of left vocal fold, Interfold ΔΦ = intravocal fold phase difference (right upper-left upper), Intrafold ΔΦ = intervocal fold phase difference (right upper-right lower); VFP = vocal fold paralysis; ML = medialization laryngoplasty; hypo AA = hypoadducted arytenoid adduction; optimal AA = optimally adducted arytenoid adduction; hyper AA = hyperadducted arytenoid adduction.

<table>
<thead>
<tr>
<th>Comparison</th>
<th>PTF</th>
<th>PTP</th>
<th>PTW</th>
<th>VE</th>
<th>% Jitter</th>
<th>% Shimmer</th>
<th>SNR</th>
<th>F0</th>
<th>Amplitude R</th>
<th>Amplitude L</th>
<th>Interfold ΔΦ</th>
<th>Intrafold ΔΦ</th>
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<tr>
<td>Normal, VFP</td>
<td>0.009</td>
<td>0.481</td>
<td>0.092</td>
<td>0.063</td>
<td>0.018</td>
<td>0.111</td>
<td>0.116</td>
<td>0.142</td>
<td>0.25</td>
<td>0.028</td>
<td>0.628</td>
<td>0.398</td>
</tr>
<tr>
<td>Normal, ML</td>
<td>0.012</td>
<td>0.014</td>
<td>0.034</td>
<td>0.063</td>
<td>&lt;0.001</td>
<td>0.011</td>
<td>0.012</td>
<td>0.4</td>
<td>0.247</td>
<td>0.039</td>
<td>0.765</td>
<td>0.26</td>
</tr>
<tr>
<td>Normal, Hypo AA</td>
<td>0.448</td>
<td>0.652</td>
<td>0.827</td>
<td>0.125</td>
<td>0.215</td>
<td>0.289</td>
<td>0.526</td>
<td>0.033</td>
<td>0.445</td>
<td>0.037</td>
<td>0.637</td>
<td>0.331</td>
</tr>
<tr>
<td>Normal, Optimal AA</td>
<td>0.847</td>
<td>0.270</td>
<td>0.813</td>
<td>0.625</td>
<td>0.8</td>
<td>0.873</td>
<td>0.334</td>
<td>0.063</td>
<td>0.363</td>
<td>0.943</td>
<td>0.903</td>
<td>0.8</td>
</tr>
<tr>
<td>Normal, Hyper AA</td>
<td>0.895</td>
<td>0.553</td>
<td>0.625</td>
<td>0.188</td>
<td>0.5</td>
<td>0.559</td>
<td>0.1</td>
<td>0.036</td>
<td>0.927</td>
<td>0.611</td>
<td>0.726</td>
<td>0.481</td>
</tr>
<tr>
<td>VFP, ML</td>
<td>0.928</td>
<td>0.679</td>
<td>0.727</td>
<td>0.56</td>
<td>0.327</td>
<td>0.956</td>
<td>0.293</td>
<td>0.387</td>
<td>0.659</td>
<td>0.284</td>
<td>0.827</td>
<td>0.619</td>
</tr>
<tr>
<td>VFP, Hypo AA</td>
<td>0.064</td>
<td>0.337</td>
<td>0.216</td>
<td>0.125</td>
<td>0.062</td>
<td>0.199</td>
<td>0.178</td>
<td>0.92</td>
<td>0.827</td>
<td>0.51</td>
<td>0.881</td>
<td>0.539</td>
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<tr>
<td>VFP, Optimal AA</td>
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<td>0.052</td>
<td>0.063</td>
<td>0.021</td>
<td>0.015</td>
<td>0.07</td>
<td>0.131</td>
<td>0.016</td>
<td>0.059</td>
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<td>0.194</td>
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<tr>
<td>VFP, Hyper AA</td>
<td>0.009</td>
<td>0.342</td>
<td>0.06</td>
<td>0.063</td>
<td>0.03</td>
<td>0.032</td>
<td>0.147</td>
<td>0.204</td>
<td>0.247</td>
<td>0.152</td>
<td>0.734</td>
<td>0.633</td>
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<tr>
<td>ML, Hypo AA</td>
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<td>0.229</td>
<td>0.173</td>
<td>0.125</td>
<td>0.046</td>
<td>0.043</td>
<td>0.073</td>
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<td>ML, Optimal AA</td>
<td>0.012</td>
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<td>0.061</td>
<td>0.063</td>
<td>0.004</td>
<td>0.006</td>
<td>0.063</td>
<td>0.125</td>
<td>0.008</td>
<td>0.022</td>
<td>0.608</td>
<td>0.125</td>
</tr>
<tr>
<td>ML, Hyper AA</td>
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<td>0.209</td>
<td>0.06</td>
<td>0.063</td>
<td>0.01</td>
<td>0.005</td>
<td>0.063</td>
<td>0.057</td>
<td>0.033</td>
<td>0.017</td>
<td>0.849</td>
<td>0.18</td>
</tr>
<tr>
<td>Hypo AA, Optimal AA</td>
<td>0.063</td>
<td>0.438</td>
<td>0.063</td>
<td>0.063</td>
<td>0.119</td>
<td>0.206</td>
<td>0.513</td>
<td>0.349</td>
<td>0.027</td>
<td>0.023</td>
<td>0.11</td>
<td>0.125</td>
</tr>
<tr>
<td>Hypo AA, Hyper AA</td>
<td>0.341</td>
<td>0.955</td>
<td>0.813</td>
<td>0.313</td>
<td>0.334</td>
<td>0.254</td>
<td>0.647</td>
<td>0.3</td>
<td>0.056</td>
<td>0.03</td>
<td>0.775</td>
<td>0.215</td>
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<tr>
<td>Optimal AA, Hyper AA</td>
<td>0.69</td>
<td>0.280</td>
<td>0.661</td>
<td>0.125</td>
<td>0.426</td>
<td>0.22</td>
<td>0.625</td>
<td>0.835</td>
<td>0.207</td>
<td>0.272</td>
<td>0.864</td>
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REFERENCES


CHAPTER 5
Preliminary investigation of adjustable balloon implant for type I thyroplasty

Matthew R. Hoffman, Rachel E. Witt,
Timothy M. McCulloch, and Jack J. Jiang

ABSTRACT

Objective: We present the adjustable balloon implant (ABI), a novel implant to be used in type I thyroplasty for the treatment of vocal fold paralysis. The ABI offers the same medialization provided by other implants, but can easily be catered to individual patient anatomy as well as modified postoperatively without the need for a revision thyroplasty.

Study design: Repeated measures with each larynx serving as its own control.

Methods: Medialization thyroplasty (MT) with the ABI was performed on five excised canine larynges. Mucosal wave, aerodynamic, and acoustic parameters were measured for three conditions: normal; right vocal fold paralysis; and paralysis with the ABI.

Results: Insertion of the ABI resulted in significant decreases in both phonation threshold pressure and phonation threshold flow. Perturbation parameters of percent jitter and percent shimmer were also significantly decreased and restored to normal levels. Signal-to-noise ratio was significantly increased to the normal level as well. The mucosal wave was preserved after implant insertion.

Conclusions: This preliminary experiment showing significant improvements in aerodynamic and acoustic parameters demonstrates the potential of the ABI as a thyroplasty implant. Effective medialization and preservation of the mucosal wave combined with post-operative adjustability makes it a potentially valuable clinical device.
INTRODUCTION

Vocal fold paralysis (VFP) is a disorder caused by damage to the recurrent laryngeal nerve (RLN) which innervates the intrinsic muscles of the larynx. VFP impairs breathing, swallowing, and vocal function (Havas 1999). A number of surgical approaches to treating VFP have been proposed, most notably injection laryngoplasty (IL), laryngeal framework surgery including type I medialization thyroplasty (MT) and arytenoid adduction (AA), and laryngeal reinnervation.

IL medializes a paralyzed vocal fold by increasing vocal fold volume. Commonly used materials include fat, collagen, micronized dermis, and calcium hydroxyapatite (Brandenburg 1992). Injections are less invasive than framework surgery and can be performed in the clinic under local anesthesia (Ford 2004). Despite the utility of IL, it has several limitations such as possible decreased mucosal wave amplitude (Gardner 1991; Hoffman 2010), absorption of the injection material into adjacent tissues (Rosen 1998), and difficulty revising incorrect injection volume or placement (Dedo 1992).

Type I thyroplasty, introduced by Isshiki (Isshiki 1974), can be employed in patients with more severe glottic insufficiency. MT has several benefits over IL, including improved preservation of the mucosal wave (Hoffman 2010; McCulloch 1998), permanence, ability to revise or remove the implant, and the ability to correct a more severe glottal gap. However, numerous challenges encountered by MT have been the subject of extensive clinical and basic science research into improving the procedure. Carving a Silastic implant during surgery can result in suboptimal shaping and prolong procedural duration (Cummings 1993; Koufman 1986; Harries 1995), resulting in increased intraoperative edema and decreased ability to judge
intraoperative voicing accurately. Several alternatives to Silastic have been proposed, including hydroxyapatite (Cummings 1993), the titanium vocal fold medializing implant (TVFMI) (Friedrich 1999), and Gore-Tex (McCulloch 1998). These implants represent valuable innovations and can be used effectively to treat VFP; however, they cannot be modified postoperatively without a revision thyroplasty. Postoperative complications such as penetration and breathy phonation due to hypoadduction or dyspnea and pressed phonation due to hyperadduction are not uncommon; therefore, being able to adjust the degree of medialization postoperatively is desirable.

Dean et al. sought to address this issue with the titanium adjustable laryngeal implant (Dean 2001). Though promising, the implant was rather complex and requires six screws to secure the implant to the thyroid cartilage. While medialization can be controlled with the micrometric screw, the limited number of implant sizes precludes complete customizability according to patient anatomy. Conversely, Gore-Tex and the TVFMI offer patient customizability but cannot be easily modified postoperatively. We present the adjustable balloon implant (ABI) which combines customizability with postoperative adjustability. Additionally, the ABI offers the benefits of traditional thyroplasty and injection laryngoplasty. It is reversible, does not alter the structure of the lamina propria, and preserves the mucosal wave as with thyroplasty. It also offers incremental medialization as with IL. A silicone balloon which can be filled with saline is introduced into the larynx via a standard thyroplasty window and stabilized with a metal frame that prevents implant extrusion and ensures the force of the implant is directed medially.
MATERIALS AND METHODS

Larynges. Five larynges were excised postmortem from canines sacrificed for non-research purposes according to the protocol described by Jiang and Titze (Jiang 1993). Canine larynges are much more widely available at our institution than human larynges. As the size and histological properties of the canine and human larynx are similar (Noordzij 1998), it is an appropriate model for studying human laryngeal physiology. Both ex vivo and in vivo canine larynges have been used previously to study interventions for vocal fold paralysis (Noordzij 1998; Czerwonka 2009; de Souza Kruschewsky 2007). There are several anatomical differences between the human and canine larynx. The thyroid and cricoid cartilages and more angulated and not as tall in the canine larynx, and there is no well-defined vocal ligament (Noordzij 1998). These differences did not negatively impact the procedure that was evaluated, as the size of the thyroid cartilage was sufficient for the creation of a thyroplasty window. Larynges were examined for evidence of trauma or disorders; any larynges exhibiting trauma or disorders were excluded. Following visual inspection, larynges were frozen in 0.9% saline solution.

Apparatus. Prior to the experiment, the epiglottis, corniculate and cuneiform cartilages, and ventricular folds of the larynx were removed to expose the true vocal folds. The superior cornu and posterosuperior part of the thyroid cartilage ipsilateral to the normal vocal fold were also removed to facilitate insertion of a lateral 3-pronged micrometer into the arytenoid cartilage. The larynx was mounted on the
apparatus (figure 1) as specified by Jiang and Titze (Jiang 1993). A metal hose clamp was used to stabilize the trachea to a tube connected to a pseudolung which served as a constant pressure source. Insertion of one 3-pronged micrometer in the arytenoid cartilage ipsilateral to the dissected thyroid cartilage allowed for adduction of one vocal fold, simulating UVFP in the unadducted vocal fold as in Czerwonka et al. (Czerwonka 2009) and Inagi et al. (Inagi 2002). Methodological consistency was maintained by always adducting the contralateral arytenoid (simulated normal) to the midline. Micrometer positioning remained constant across sets of trials within the same larynx. Tension on the vocal folds and control of vocal fold elongation was accomplished by connecting the thyroid cartilage, just inferior to the thyroid notch, to an anterior micrometer. Vocal fold elongation and adduction remained constant for all trials.

The pseudolung used to initiate and sustain phonation in these trials was designed to simulate the human respiratory system. Pressurized airflow was passed through two Concha Therm III humidifiers (Fisher & Paykel Healthcare Inc., Laguna Hills, California) in series to humidify and warm the air. The potential for dehydration was further decreased by frequent application of 0.9% saline solution between trials. Airflow was controlled manually and measured using an Omega airflow meter (model FMA-1601A, Omega Engineering Inc., Stamford, Connecticut). Pressure measurements were taken immediately before the air passed into the larynx using a Heise digital pressure meter (901 series, Ashcroft Inc., Stratford, Connecticut).

Acoustic data were collected using a dbx microphone (model RTA-M, dbx Professional Products, Sandy, Utah) positioned at a 45° angle to the vocal folds. The microphone was placed approximately 10 cm from the glottis to minimize acoustic noise produced by turbulent airflow.
Acoustic signals were subsequently amplified by a Symetrix preamplifier (model 302, Symetrix Inc., Mountlake Terrace, Washington). A National Instruments data acquisition board (model AT-MIO-16; National Instruments Corp, Austin, Texas) and customized LabVIEW 8.5 software were used to record airflow, pressure, and acoustic signals on a personal computer. Aerodynamic data were recorded at a sampling rate of 100 Hz and acoustic data at 40,000 Hz. Experiments were conducted in a triple-walled, sound-proof room to reduce background noise and stabilize humidity levels and temperature.

The vocal fold mucosal wave was recorded for approximately 200 milliseconds per trial using a high-speed digital camera (model Fastcam-ultima APX; Photron, San Diego, CA). Videos were recorded with a resolution of 512 x 256 pixels at a rate of 4000 frames/second.

**Adjustable balloon implant.** The implant (figure 2) was manufactured by Hood Laboratories (Pembrooke, MA) based on the authors’ design. A round balloon with diameter of 12 mm and wall thickness of 0.5 mm was connected via tubing to a luer slip one-way check valve. The tubing had an outside diameter of 1.5 mm. Both the balloon and tubing were made using 50 durometer medical grade silicone. The implant was placed lateral to the thyroarytenoid muscle (figure 2) and secured inside the larynx using an aluminum frame (figure 3). The selected frame was suitable for five larynges of differing size used in this study; however, multiple frame sizes could easily be made to accommodate small or large larynges.
Although aluminum was used in this preliminary study on excised canine larynges, the frame would be manufactured from titanium if the implant were applied to human patients. Superior and inferior flanges prevented extrusion of the implant while lateral flanges with holes allowed the frame to be sutured to the thyroid lamina.

A balloon with maximum volume of 1.5 cc was used for all larynges. The selected size was based on knowledge of volume required for effective injection laryngoplasty, with added volume to compensate for the manipulations to the larynx made when creating the thyroplasty window. A main advantage of the ABI is that the size of the balloon is not as important as the volume of saline injected into it. While only one implant was used in this study, it worked for a variety of larynges. The amount of saline injected depended upon the size of the larynx and width of the glottal gap. Saline was injected into the balloon via a luer slip syringe until the paralyzed fold approximated the normal fold. Fine adjustments were then made according to perceptual analysis of vocal quality and quantitative analysis of threshold aerodynamics. Care was taken to avoid overinjection and resultant balloon bulging. If bulging was observed, saline was removed until an optimal volume was reached.

**Experimental Methods.** Trials were conducted as a sequence of 5 second periods of phonation, followed by 5 second periods of rest. Five trials were performed for each condition. To simulate normal, both arytenoids were adducted with lateral prongs. To simulate unilateral VFP, only the left arytenoid was adducted to the midline; the right was left unadducted. This
same setup was used for the ABI condition, but the implant was inserted and filled to an optimal volume. During each trial, airflow passing through the larynx was increased gradually and consistently until the onset of phonation. Larynges were thoroughly hydrated with 0.9% saline solution between trials and between sets of trials to eliminate any potentially confounding effects of dehydration.

**Data Analysis.** Phonation was evaluated in three conditions: normal; simulated right VFP; and right VFP with the ABI. Airflow and pressure at the phonation onset were recorded as the phonation threshold flow (PTF) and phonation threshold pressure (PTP), respectively. Phonation threshold power (PTW) was calculated as the product of these values. PTF, PTP, and PTW were determined manually using customized LabVIEW 8.5 software. Aerodynamic parameters were used to provide information on vocal effort and glottal gap.

Measured acoustic parameters included fundamental frequency ($F_0$), signal-to-noise ratio (SNR), percent jitter, and percent shimmer. Acoustic signals were trimmed to produce three 1-second segments per trial using GoldWave 5.1.2600.0 software (GoldWave Inc., St. John’s, Canada) and these segments were analyzed using TF32 software (Madison, WI).

High speed video recordings of the mucosal wave were analyzed using a customized MATLAB program (The MathWorks, Natick, MA). Vibratory properties of each of the four vocal fold lips (right-upper, right-lower, left-upper, left-lower) were quantified via digital videokymography (VKG). VKG represents a valuable research tool which can quantify the mucosal wave. Threshold-based edge detection, manual wave segment extraction, and non-linear least squares curve fitting using the Fourier Series equation were applied to determine the most closely fitting sinusoidal curve. This curve was used to derive the amplitude and phase difference
of the mucosal wave of each vocal fold lip, both before and after treatment. Mucosal wave amplitude was calculated as the average of the amplitudes of the upper and lower paralyzed vocal fold lips. While only relative rather than absolute values could be obtained due to current technological limitations, this was sufficient for pre-/post-treatment comparisons.

**Statistical analysis.** One-way repeated measures analysis of variance (ANOVA) was performed to determine if there were differences in the parameters of interest across the three conditions. Paired t-tests were performed to determine if significant differences occurred between paired conditions (normal and VFP, VFP and ABI, normal and ABI). If data were not normal according to a Shapiro-Wilk test or did not display equal variance according to a Levene’s test, an ANOVA on ranks or Wilcoxon-Mann-Whitney paired rank sum test was performed. Tests were two-tailed and a significance level of $\alpha=0.05$ was used.

**RESULTS**

**Aerodynamics.** Summary data are presented in table 1. Inserting the ABI significantly decreased PTP ($p = 0.038$), PTF ($p < 0.001$), and PTW ($p = 0.016$) relative to the VFP condition (table 2; figure 4). PTF ($p = 0.039$) and PTW ($p = 0.038$) remained significantly higher relative to normal (table 2).
Acoustics. Summary data are presented in table 1. The ABI had significant effects on SNR (p = 0.005), percent jitter (p = 0.034), and percent shimmer (p = 0.037) (table 2; figure 5). These values were restored to the levels observed for the normal condition (tables 1, 2).

Mucosal wave. Summary data are presented in table 1. Mucosal wave amplitude of the normal fold discernibly increased from the normal to paralyzed condition (p = 0.055). Amplitude of this fold remained elevated after insertion of the implant (table 1; figure 6). Amplitude of the right vocal fold (simulated paralysis) was the same in the normal and ABI conditions (p = 0.966).

DISCUSSION

We present a novel implant for type I thyroplasty which offers customizability according to patient anatomy as well as postoperative adjustability. Even at this preliminary prototypical stage, the implant provided effective medialization which improved vocal performance.

Glottal gap was decreased upon insertion of the ABI, placing the paralyzed vocal fold in a position more conducive for voicing and increasing phonatory efficiency. PTP, PTF, and PTW were all significantly
decreased, though not to the levels observed for the normal condition. This can likely be attributed to a slight posterior glottal gap caused by the round shape of the implant. Such a posterior glottal chink could be corrected with an arytenoid adduction. Evaluating the effect of combined arytenoid adduction with ABI thyroplasty will be the subject of future study.

The ABI not only improved the acoustic parameters of interest, but also restored SNR, percent jitter, and percent shimmer to normal or near normal levels. While it did increase F₀, the resultant frequency was discernibly, though not significantly, less than normal. Improvement of perturbation parameters to approximately normal levels can be attributed to restoration of vocal fold contact and vibrational periodicity. Increased SNR occurred due to decreased airflow required for phonation as well as increased acoustic output.

Interestingly, insignificant increases in the mucosal wave amplitude of the right and left vocal folds were observed from the normal to paralyzed condition. Based on experimental observations, this appeared to be due to the high airflow through the glottis required for phonation. However, without vocal fold contact, vocal quality was poor despite the large amplitude. Insertion of the ABI closed the glottal gap and preserved mucosal wave amplitude, resulting in improved vocal quality. Following insertion of the ABI, the mucosal wave was preserved.

There are several limitations to the experimental design and implant which will be the subject of future investigations. While the excised larynx setup is a valuable research tool and has been used frequently to study VFP (Hoffman 2010; Noordzij 1998; Czerwonka 2009; Inagi 2002; Witt 2010), it cannot simulate all clinical concerns of thyroplasty such as physiological tissue response to implant insertion and long-term effectiveness of the implant. Second, a round
balloon was used in this study which has the natural tendency to expand uniformly in all
directions. This was mitigated by the use of the aluminum frame, which compressed the balloon
superiorly and inferiorly, ensuring that the primary force of the balloon on the vocal fold was
directed medially. Third, though silicone is a widely used in medical applications including
thyroplasty, allergic reaction has been reported (Hunsaker 1995). Covering the implant with a
biointegratable material such as Gore-Tex could address this concern, preserving the advantages
of the ABI while eliminating the possibility of an adverse reaction. Continued use of the excised
larynx setup will allow us to evaluate implant modifications objectively and quickly before they
are applied to human patients.

Application of the ABI to human patients would require several steps not required for this
preliminary excised larynx experiment. After insertion of the implant, two to three centimeters of
tubing would be left protruding from the balloon to allow for postoperative adjustments to
implant volume. The tubing would be sealed with surgical glue prior to closure of the surgical
site. Tubing could be left external to the skin similar to a wound drainage tube or, alternatively,
left along the inferior margin of the thyroid cartilage. A minor incision at the anteroinferior
aspect of the thyroid cartilage would allow for access to the tubing, while blue prolene suture
attached to the most distal aspect of the tubing could facilitate visualization. Initial closure of the
implant tubing is accomplished with a one-way valve and distal occlusion of the tube lumen with
surgical glue. Adjusting the volume can be accomplished by severing the tubing proximal to the
seal, increasing or decreasing the amount of saline injected, and then re-occluding the lumen
with surgical glue.
To increase procedural effectiveness and the simplicity of ABI insertion, implant and methodological modifications will be evaluated. The spherical balloon shape used in this study is the primary limitation of the ABI. Using a wedge-shaped balloon instead could close the posterior glottal chink as well as prevent overadduction at the anterior commissure. This could also eliminate the need for the supporting frame, opening up the possibility for implant insertion via an anterior microthyrotomy approach. Standard landmarks used in traditional thyroplasty such as the inferior margin of the thyroid cartilage and the anterior commissure could be used to ensure proper vertical placement is maintained. Such an approach would not require the traditional large neck incision currently used for thyroplasty and may also prevent cracking of the thyroid cartilage, particularly in elderly patients, that can occur when making a thyroplasty window. This procedure would be easily reversible, as only a small hole in the anterior thyroid lamina would be needed for implant insertion.

While these modifications could be valuable as the ABI is improved, it is important to note the advantages of the ABI even at this early stage. One implant was used for all larynges in this study, which included specimens of varying size, and provided adequate medialization in all cases. The ABI was easy to insert and required no pre- or intraoperative modifications, such as carving with a Silastic implant. It was easy to adjust medialization incrementally and determine the optimal degree of medialization for a superior vocal outcome (figure 7). If excess saline was

Figure 7. Incremental adjustments to the volume of saline injected into the implant. A) larynx with simulated right vocal fold paralysis; B) larynx with the implant inserted but no saline injected; C) 0.4 cc injected; D) 0.6 cc injected; E) 1.0 cc injected; F) 1.2 cc injected.
injected and pressed phonation resulted, the excess could easily be removed until optimal vocal quality returned. As modifications to the ABI are made, these benefits will be preserved.

**CONCLUSION**

A novel implant for type I thyroplasty is presented that has the potential to offer patient customizability and postoperative adjustability. The ABI provided adequate medialization while significantly decreasing the aerodynamic power required for vocal fold vibration, restoring acoustic parameters to normal levels, and preserving the mucosal wave. Though the potential of the ABI has been demonstrated in this preliminary excised larynx experiment, it has not yet been tested in human patients. Modifications to implant shape and insertion method could increase its clinical utility and will be the subject of future research.

**ACKNOWLEDGEMENTS**

The authors thank Mr. Dennis Creedon and Hood Laboratories for their contributions to the construction of the adjustable balloon implant. The authors also thank Adam Rieves and James Madsen for their help creating the images presented in this paper. This study was funded by NIH grant numbers R01 DC008153, R01 DC05522, and R01 DC008850 from the National Institute on Deafness and other Communicative Disorders.

**TABLES**

Table 1. Summary aerodynamic, acoustic, and mucosal wave data including p-values obtained from one-way repeated measures analysis of variance (ANOVA) statistical tests. VFP = vocal fold paralysis; ABI = adjustable balloon implant; PTF = phonation threshold flow; PTP =
phonation threshold pressure; $F_0$ = fundamental frequency; SNR = signal-to-noise ratio; R = right vocal fold (simulated paralysis in VFP and ASI conditions); L = left vocal fold. Asterisks indicate significant p-values.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal</th>
<th>VFP</th>
<th>ABI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTF (ml/s)</td>
<td>17.12 ± 6.86</td>
<td>99.12 ± 57.51</td>
<td>25.08 ± 4.14</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>PTP (cmH₂O)</td>
<td>7.976 ± 3.38</td>
<td>20.72 ± 11.88</td>
<td>10.71 ± 5.09</td>
<td>0.002*</td>
</tr>
<tr>
<td>PTW (cmH₂O*ml/s)</td>
<td>142.8 ± 88.9</td>
<td>2298 ± 2355</td>
<td>281.9 ± 167.7</td>
<td>0.002*</td>
</tr>
<tr>
<td>$F_0$ (Hz)</td>
<td>306 ± 96</td>
<td>177 ± 26</td>
<td>246 ± 45</td>
<td>0.024*</td>
</tr>
<tr>
<td>SNR</td>
<td>13.71 ± 4.94</td>
<td>3.945 ± 1.94</td>
<td>13.43 ± 4.06</td>
<td>0.003*</td>
</tr>
<tr>
<td>Percent jitter</td>
<td>1.089 ± 0.98</td>
<td>3.156 ± 1.38</td>
<td>0.968 ± 0.480</td>
<td>0.024*</td>
</tr>
<tr>
<td>Percent shimmer</td>
<td>19.26 ± 4.99</td>
<td>49.41 ± 19.1</td>
<td>21.47 ± 4.91</td>
<td>0.007*</td>
</tr>
<tr>
<td>Amplitude (R)</td>
<td>3.794 ± 1.93</td>
<td>4.511 ± 1.62</td>
<td>3.878 ± 3.92</td>
<td>0.367</td>
</tr>
<tr>
<td>Amplitude (L)</td>
<td>3.509 ± 1.22</td>
<td>6.812 ± 2.17</td>
<td>6.176 ± 5.65</td>
<td>0.275</td>
</tr>
</tbody>
</table>

Table 2. P-values obtained from paired t-tests between treatments. VFP = vocal fold paralysis; ABI = adjustable balloon implant; PTF = phonation threshold flow; PTP = phonation threshold pressure; $F_0$ = fundamental frequency; SNR = signal-to-noise ratio; R = right vocal fold (simulated paralysis in VFP and ABI conditions); L = left vocal fold. Asterisks indicate significant p-values.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal, VFP</th>
<th>VFP, ABI</th>
<th>Normal, ABI</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTP (cmH₂O)</td>
<td>0.007*</td>
<td>0.038*</td>
<td>0.103</td>
</tr>
<tr>
<td>PTF (ml/s)</td>
<td>&lt;0.001*</td>
<td>&lt;0.001*</td>
<td>0.039*</td>
</tr>
<tr>
<td>PTW (cmH₂O*ml/s)</td>
<td>0.016*</td>
<td>0.016*</td>
<td>0.038*</td>
</tr>
<tr>
<td>$F_0$ (Hz)</td>
<td>0.044*</td>
<td>0.069</td>
<td>0.169</td>
</tr>
<tr>
<td>SNR</td>
<td>0.018*</td>
<td>0.005*</td>
<td>0.901</td>
</tr>
<tr>
<td>Percent jitter</td>
<td>0.092</td>
<td>0.034*</td>
<td>0.733</td>
</tr>
<tr>
<td>Percent shimmer</td>
<td>0.031*</td>
<td>0.037*</td>
<td>0.349</td>
</tr>
<tr>
<td>Amplitude (R)</td>
<td>0.597</td>
<td>0.735</td>
<td>0.966</td>
</tr>
<tr>
<td>Amplitude (L)</td>
<td>0.055</td>
<td>0.777</td>
<td>0.813</td>
</tr>
</tbody>
</table>

REFERENCES


ABSTRACT

Objective: Laryngeal function can be evaluated from multiple perspectives, including aerodynamic input, acoustic output, and mucosal wave vibratory characteristics. To determine the classifying power of each of these, we used a multilayer perceptron artificial neural network (ANN) to classify data as normal, glottic insufficiency, or tension asymmetry.

Study design: Case series analyzing data obtained from excised larynges simulating different conditions.

Methods: Aerodynamic, acoustic, and videokymographic data were collected from excised canine larynges simulating normal, glottic insufficiency, and tension asymmetry. Classification of samples was performed using a multilayer perceptron ANN.

Results: A classification accuracy of 84% was achieved when including all parameters. Classification accuracy dropped below 75% when using only aerodynamic or acoustic parameters and below 65% when using only videokymographic parameters.

Conclusions: Samples were classified with the greatest accuracy when using a wide range of parameters. Decreased classification accuracies for individual groups of parameters demonstrate the importance of a comprehensive voice assessment when evaluating dysphonia.
INTRODUCTION

Voice production is a complex physiological process requiring integration of the nervous system, respiratory tract, and larynx. Accordingly, dysphonia is multidimensional in nature, with different pathologic processes affecting different aspects of the voice (Aboras 2010; Yu 2001). Despite this complexity, assessment is primarily perceptual and often consists of subjective interpretation of vocal quality and stroboscopic exams. Perceptual assessment is regarded as the gold standard (Ma 2006); however, it is imprecise and unreliable when analyzing the results of a therapeutic intervention or when comparing patient groups (Hakkesteegt 2008). A widely used metric to evaluate vocal health, the GRBAS (grade, roughness, breathiness, asthenia, strain) scale, lacks detail and sensitivity (Hartl 2003) and displays only low to moderate interrater reliability (Hakkesteegt 2008; de Bodt 1997; Dejonckere 1998). The low temporal resolution of videostroboscopy is adequate when evaluating periodic vocal fold vibration, but cannot reliably evaluate the aperiodic vocal fold vibration which is characteristic of dysphonia (Krausert 2011; Patel 2008). A systematic approach implementing a series of objective, quantitative methods is warranted.

Quantitative acoustic measurements are a common assessment method used to evaluate vocal pathology (Titze 1995). Acoustic measures are valuable and provide different information about laryngeal function than self-assessment (Hanschmann 2011). However, acoustic parameters do not provide a global assessment and cannot predict severity of dysphonia (Yu 2001). Also, single acoustic parameters display poorer correlation than a combination of several objective parameters with perceptual analysis (Hakkesteegt 2008).
Aerodynamic assessment provides important information on the inputs to normal and disordered phonation (Baken 2000) and the effort required to produce voice. Aboras et al. measured acoustic and aerodynamic parameters and found that subglottal pressure was the only measure which was predictive of a patient's self-perception of dysphonia (Aboras 2010). Though valuable, aerodynamic measurements alone cannot describe vocal fold vibratory characteristics or resultant sound quality.

To provide a complete picture of vocal health and laryngeal function, a range of parameters must be considered simultaneously. While such an assessment would certainly provide valuable information, the number of parameters would also make analysis laborious. An algorithm for efficient, automated data interpretation would be valuable and could potentially facilitate widespread clinical application. Classification models, including artificial neural networks (ANNs), are powerful mathematical models which can classify data according to nonlinear statistical analysis (Cross 1995). Further, ANNs can handle extremely large data sets. Of particular interest to this study, they can be used to determine the classifying power of individual parameters and groups of parameters.

The multilayer perceptron (MLP) is one type of ANN and is the most commonly used in medical applications (Bishop 1995). It consists of an input layer that receives data, at least one hidden layer, and an output layer which provides the classification result. Data are presented to the input layer, computations are performed in the hidden layers, and an output value is obtained at each node of the output layer (Yan 2006). These values determine the class into which the data set is classified. Before an ANN can be used to classify an unlabeled data set, it must be trained. Back propagation is one of the most common methods of training for an MLP (Rumelhart 1986).
and minimizes the mean-square error of the output for the training set (Cross 1995). During the learning process, weights associated with connections between nodes are varied with the objective of decreasing the mean-square error of the output (Cross 1995; Ruck 1990). The more input parameters and examples in the training set that are included, the better the ANN typically performs. The ability to synthesize a large amount of information and provide a simple output is a key benefit relevant to medical decision-making and specifically, multi-parameter voice assessment.

We extracted feature vectors containing aerodynamic, acoustic, and videokymographic parameters from excised larynx experiments simulating normal and various severities of glottic insufficiency, simulating recurrent laryngeal nerve paralysis (RLNP), and tension asymmetry, simulating superior laryngeal nerve paralysis (SLNP). A machine learning algorithm was used to train the multilayer perceptron neural network, which was then used to classify the data. The number of hidden nodes was modified to achieve a higher correct classification rate, and the components of the feature vector were examined to consider their individual contribution to classification. We hypothesized that classification accuracy would be higher with a larger number of parameters.

**MATERIALS AND METHODS**

*Larynges.* Thirty-two larynges were excised postmortem from canines sacrificed for non-research purposes according to the protocol described by Jiang and Titze (Jiang 1993). Canine larynges are much more widely available at our institution than human larynges and have been used extensively to study laryngeal physiology (Noordzij 1998; Alipour 2007). There are several
anatomical differences between the human and canine larynx. The thyroid and cricoid cartilages are more angulated and not as tall in the canine larynx, and there is no well-defined vocal ligament (Noordzij 1998). These differences did not negatively impact the study. Larynges were examined for evidence of trauma or disorders and any larynges exhibiting trauma or disorders were excluded. Following visual inspection, larynges were frozen in 0.9% saline solution.

Classification ability generally improves as more data are included in the analysis (Daelemans 2002). To increase the amount of data, we used both previously collected (Hoffman 2010; Hoffman 2011; Hoffman 2011; Devine 2012) and newly collected data. In total, 389 trials from 32 larynges were included. Of the 389 trials, 179 simulated normal, 100 simulated tension asymmetry (representative of superior laryngeal nerve paralysis), and 110 trials simulated glottic insufficiency (representative of recurrent laryngeal nerve paralysis).

**Apparatus.** Prior to the experiment, the supraglottic tissues were removed to expose the true vocal folds. The superior cornu and posterosuperior part of the thyroid cartilage were also removed to facilitate insertion of a lateral 3-pronged micrometer into the arytenoid cartilage. The larynx was mounted on the apparatus (figure 1) specified by Jiang and Titze (Jiang 1993). A metal hose clamp stabilized the trachea to a tube connected to a constant pressure source, or pseudolung. The pseudolung was designed to simulate the human respiratory system. Pressurized airflow was passed through two Concha Therm III humidifiers (Fisher & Paykel Healthcare Inc., Laguna Hills, California) in
series to humidify and warm the air. The potential for dehydration was further decreased by application of 0.9% saline between trials. Airflow was controlled manually and measured using an Omega airflow meter (model FMA-1601A, Omega Engineering Inc., Stamford, Connecticut). Pressure measurements were recorded immediately before the air passed into the larynx using a Heise digital pressure meter (901 series, Ashcroft Inc., Stratford, Connecticut).

Acoustic data were collected using a dbx microphone (model RTA-M, dbx Professional Products, Sandy, Utah) placed at a 45° angle to the vocal folds. The microphone was placed approximately 10 cm from the glottis to minimize acoustic noise produced by turbulent airflow. Acoustic signals were subsequently amplified by a Symetrix preamplifier (model 302, Symetrix Inc., Mountlake Terrace, Washington). A National Instruments data acquisition board (model AT-MIO-16; National Instruments Corp, Austin, Texas) and customized LabVIEW 8.5 software were used to record aerodynamic and acoustic signals. Aerodynamic data were recorded at a rate of 100 Hz and acoustic data at 40,000 Hz. Experiments were conducted in a triple-walled, sound-attenuated room to reduce background noise and stabilize humidity and temperature.

The vocal fold mucosal wave was recorded for approximately 200 milliseconds per trial using a high-speed camera (model Fastcam-ultima APX; Photron, San Diego, CA). Videos were recorded with a resolution of 512 x 256 pixels at a rate of 4000 frames/second.

**Experimental Methods.** Trials were conducted as a sequence of 5 second periods of phonation followed by 5 seconds of rest. Five trials were performed for each condition. To simulate normal, both arytenoids were adducted with lateral prongs and the vocal folds were elongated via a suture placed at the midline of the thyroid cartilage, just superior to the vocal folds. This approach was also used for the larynges simulating glottic insufficiency. To simulate
glottic insufficiency, only the left arytenoid was adducted to the midline; the right was left unadducted (figure 2a) (Czerwonka 2009). The size of the glottal gap was varied across trials and larynges to simulate paralysis of differing severity.

The method described in Devine et al. was used to simulate tension asymmetry (Devine 2012). Asymmetry was created using weights which simulated cricothyroid muscle function. The cricothyroid muscle bellies were dissected away to facilitate suture placement. Insertion points for the muscles were noted as fibers were removed. Placement of the sutures and resulting force vectors can be seen in figure 2b. A suture fixing the cricoid cartilage to the trachea was first placed along the midline; this prevented displacement of the cricoid relative to the trachea due to the force of the weights. Sutures simulating the oblique and vertical bellies were inserted at the center of insertion of each belly on the thyroid cartilage and extended along the line of action of the muscle. After unilateral suture placement, the distance and angle between the suture line and the midline of the larynx were measured. The angle of the vertical belly was zero since these sutures were set parallel to the midline. These measurements were then translated to the other side of the larynx to maintain symmetry. Suture angle and the thyroid insertion point were equivalent between sides since the motion of the thyroid cartilage (relative
to the cricoid cartilage) was the targeted output of suture forces. Suture placement is shown in figure 2. During tension asymmetry trials, weights were only placed on the sutures corresponding to the left cricothyroid muscle bellies. The mass of the weights was varied across trials and larynges to simulate paralysis of differing severity.

**Data analysis.** Airflow and pressure at the phonation onset were recorded as the phonation threshold flow (PTF) and phonation threshold pressure (PTP), respectively. Phonation threshold power (PTW) was calculated as the product of these values. PTF, PTP, and PTW were determined manually using customized LabVIEW 8.5 software.

Measured acoustic parameters included fundamental frequency ($F_0$), signal-to-noise ratio (SNR), percent jitter, and percent shimmer. Acoustic signals were trimmed to produce three 1-second segments per trial using GoldWave 5.1.2600.0 software (GoldWave Inc., St. John’s, Canada) and these segments were analyzed using TF32 software (Madison, WI).

High speed video recordings of the mucosal wave were analyzed using a customized MATLAB program (The MathWorks, Natick, MA). Vibratory properties of the four vocal fold lips (right upper, right lower, left upper, left lower) were quantified via digital videokymography. Threshold-based edge detection, manual wave segment extraction, and non-linear least squares curve fitting using the Fourier Series equation were applied to determine the most closely fitting sinusoidal curve. This curve was used to derive the amplitude and phase difference of the mucosal wave for each vocal fold lip. Mucosal wave amplitude was calculated as the average of the amplitudes of the upper and lower vocal fold lips. While only relative rather than absolute values could be obtained due to current technological limitations, this was sufficient for comparisons across conditions.
**Data processing.** MATLAB software including the Neural Network Toolbox (The MathWorks) was used for all data processing. In total, 389 trials were analyzed and the derived feature sets were used as a basis for determining models of normal, glottic insufficiency, and tension asymmetry voice production. By attaching the known status of a trial to its feature vector, machine learning techniques can be applied with the goal of modeling the relationship between the input features and the classification of a given trial. The data were randomly split 70/15/15 into training, validation, and test sets, respectively. This division is recommended by the software and is also a common split used in the field. Using 99% of the data in the training set may train the model well, but the resulting classification system would likely be poorly generalizable. Conversely, using a small percentage of the data during training may ensure the system is generalizable, but it would likely perform poorly.

The ANN is presented with the known data, goes through a training and validation stage, and finally is presented with new data during a test stage. The training data and testing data are kept separate in order to evaluate the generalizing ability of the classification.

Data were normalized with each variable in the data set ranging from -1 to 1, with a mean of 0 and a standard deviation of 1. Normalizing data improves the efficiency and accuracy of the classification algorithm (Saarinen 1993). As random influences may occur during the partitioning process, a more stable
performance measurement was obtained by repeating each classification task ten times and averaging over the individual results. Classification rates were calculated based on evaluations occurring during all stages of the machine learning process. A standard multi-layer perceptron (figure 3) was created using sigmoidal activation functions in one hidden layer, and the number of nodes in the hidden layer was varied in increments of 20 from N=20 to N=200. An upper limit of 200 was selected because using a number of hidden nodes significantly higher than one half of the number of data points can adversely affect generalization. A scaled conjugate backpropagation learning algorithm was used. The goal of the learning algorithm in this model is to modify the weights associated with the connections between the nodes (represented by lines in figure 3) such that an input vector will produce the specified desired output vector.

Separate from the variation of models, the feature set was selectively reduced in an attempt to discover the classification ability of individual parameters and subgroups of parameters. This included the categorical elimination of aerodynamic, acoustic, and videokymographic parameters. In addition to their inclusion in these subsets, all parameters were used on their own as a singular input. The number of hidden nodes in these analyses was determined based on the number attaining the highest classification accuracy when considering all parameters.

*Receiver operating characteristic analysis.* To determine the ability of the ANN to correctly analyze normal, glottic insufficiency, and tension asymmetry trials, receiver operating characteristic (ROC) analysis was performed and area under the curve (AUC) was determined.

**RESULTS**
Summary data are provided in table 1. Overall classification accuracy was 84.02 ± 1.90%, including 83.58 ± 3.95% for normal trials, 70.56 ± 5.78% for tension asymmetry trials, and 98.11 ± 0.28% for glottic insufficiency trials (table 2). These classification rates corresponded to the use of 180 hidden nodes. Total classification rates varied from a minimum of approximately 82% with 20 and 200 hidden nodes to the maximum of 84% when using 180 hidden nodes. Classification accuracy was 74.33 ± 2.05% when using only aerodynamic parameters, 73.25 ± 2.55% when using only acoustic parameters, and 64.22 ± 2.56% when using only videokymographic parameters (table 2). Phonation threshold flow (PTF) demonstrated the greatest individual classification accuracy at 73.91 ± 2.02%.

ROC analysis yielded curves with AUC of 0.8795 for normal (figure 4a), 0.6639 for SLNP (figure 4b), and 0.9878 for glottic insufficiency (figure 4c).

**DISCUSSION**

Classification accuracy was highest when including all parameters and decreased when considering single groups of parameters or pairs of groups. As expected, classification rates were lower for individual parameters, ranging from 52% (interfold mucosal wave phase difference) to
nearly 74% (phonation threshold flow). Interestingly, the classification rate of phonation threshold flow approached that of the aerodynamic parameters as a group, indicating airflow was the most distinguishing parameter in this set of data. As airflow is more sensitive than pressure to changes in glottal abduction (Hottinger 2007), it could be expected to classify glottic insufficiency effectively. It did not, however, differentiate well between normal and tension asymmetry, though symmetric elongation-dependent changes in phonation threshold flow have been reported (Jiang 2008). Signal-to-noise ratio displayed a similar classification pattern, classifying normal and glottic insufficiency effectively while displaying very limited ability to detect tension asymmetry. Signal-to-noise ratio is a good parameter to describe glottic insufficiency, as the presence of a wide glottal gap decreases the signal (voice) and increases the noise (turbulent airflow). This parameter is not as useful in distinguishing between subtle differences caused by asymmetric vocal fold elongation.

Consistently high classification rates were predictably observed for glottic insufficiency. As the normal and tension asymmetry conditions are more similar to each other than either is to glottic insufficiency, a high classification rate is expected. Aerodynamic and acoustic parameters displayed high group classification rates. Although the classifying ability of videokymographic parameters was lower, classification of both aerodynamic and acoustic parameters improved when coupled with information on the vibratory characteristics of the mucosal wave. This finding also illustrates an important point about artificial neural network analysis: including more parameters generally increases classifying power. While an individual parameter such as mucosal wave amplitude may not distinguish among groups in isolation, evaluating it in relation to other parameters can improve the ability to identify a given condition. Additionally,
classification rates for mucosal wave parameters (vibratory amplitude, phase difference) may have been relatively low because they are not the optimal parameters to describe superior and recurrent laryngeal nerve paralyses. While the parameters used in this study were selected because they could be applied clinically with minimal difficulty, complex parameters such as global entropy and correlation length provided by spatiotemporal analysis (Zhang 2007) may better describe irregular vocal fold vibration. Pursuing methods which can expedite the extraction of these parameters to facilitate clinical application is warranted.

Two main limitations will be the subject of future studies. First, it may be interesting to evaluate more complex voice parameters such as those provided by spatiotemporal analysis or nonlinear dynamic acoustic analysis. These measures may prove more valuable than some of the parameters included in this study such as percent jitter and shimmer, which, though capable of distinguishing between normal and glottic insufficiency here as well as between normal and vocal fold polyps in a previous study (Jiang 2009), cannot identify more subtle voice disorders such as nodules or tension asymmetry. Patient-based measures such as the voice handicap index could also be included, if it was found that inclusion of this subjective assessment augmented classification accuracy. Including these parameters in future analyses may improve the ability to distinguish among normal and various voice disorders. Second and most importantly, data from excised larynx experiments rather than human patients were used. This was done to allow us to examine a wide range of parameters that are not typically collected in the clinical setting. Phonation threshold power, for example, has not yet been measured clinically. Using data from excised larynx experiments also provided more inputs than could be usually included if using data from human subjects; however, the excised larynx model can only approximate the dynamic
conditions which occur in living patients. Specifically, we could not simulate the effects of thyroarytenoid contraction, vocal fold asymmetry due to paralysis-induced muscle atrophy, or compensatory phenomena. While the models of glottic insufficiency and tension asymmetry used in this study have been applied previously (Noordzij 1998; Devine 2012; Czerwonka 2009), they do not encapsulate the subtleties of the clinical entities which they represent.

While perceptual analysis and patient self-reporting are frequently used to evaluate dysphonia in the clinic, they are subjective and can introduce bias into treatment decisions (Carding 2009). The quantitative parameters in this study which best parallel perceptual analysis are likely fundamental frequency and perturbation measurements. Though valuable as part of a more comprehensive voice evaluation, these parameters exhibited individual classification rates between 59 and 68%. This is much lower than the overall classification rate of 84% when considering all parameters. The importance of considering multiple parameters is particularly evident when evaluating tension asymmetry. The aforementioned acoustic parameters displayed classification rates of 13-25%, compared to nearly 71% for the entire feature set. Diagnosis of superior laryngeal nerve paralysis is difficult (Dursun 1996) and recurrent laryngeal nerve paralysis is likely underdiagnosed (Myssiorek 2004). Developing a standardized comprehensive, multiparameter assessment may aid in the evaluation of these disorders.

There is a wide spectrum of vocal dysfunction (Painter 1990) and no single parameter can adequately characterize vocal quality or dysphonia severity (Ma 2006). An admitted limitation of quantitative multiparameter assessment is the time required to record the range of measurements; however, noninvasive devices such as the airflow interrupter (Jiang 1999) or KayPENTAX Phonatory Aerodynamic System can record seven of the eleven parameters used in this study in
less than one minute. Videokymographic analysis of high-speed video images could be performed in an additional few minutes, and even less as improved automated analysis techniques are developed (Jiang 2008). Employing artificial neural network analysis eliminates the most time-consuming aspect of the process – data interpretation. If this method is applied on a larger scale, databases could be generated which could then serve as inputs, thus increasing the classifying power of the algorithm and allowing for a more complex classification scheme with more disorders included.

CONCLUSION

Superior classification rates obtained with a multiparameter assessment compared to subgroup or individual parameter results demonstrate the value of a comprehensive voice assessment. Individual parameter classification rates, particularly for superior laryngeal nerve paralysis, were rather low. Considering a wide range of parameters as well as the relationships among those parameters allows for an evaluation of laryngeal function from multiple perspectives. Additional work developing new parameters able to improve current classification rates as well as automated extraction of these parameters would be beneficial.

ACKNOWLEDGEMENTS

This study was funded by NIH grant numbers R01 DC008153, R01 DC05522, R01 DC008850, and T32 DC009401 from the National Institute on Deafness and other Communicative Disorders.
Table 1. Summary data from the three groups. Values are presented as mean ± standard deviation. SLNP = superior laryngeal nerve paralysis; RLNP = recurrent laryngeal nerve paralysis; PTP = phonation threshold pressure; PTF = phonation threshold flow; PTW = phonation threshold power; $F_0$ = fundamental frequency; SNR = signal-to-noise ratio; VKG = videokymography.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal</th>
<th>Tension asymmetry</th>
<th>Glottic insufficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aerodynamic parameters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTP (cmH2O)</td>
<td>14.58 ± 6.84</td>
<td>20.61 ± 13.37</td>
<td>19.36 ± 8.40</td>
</tr>
<tr>
<td>PTF (L/min)</td>
<td>27 ± 15</td>
<td>25 ± 15</td>
<td>122 ± 40</td>
</tr>
<tr>
<td>PTW (cmH2O*L/min)</td>
<td>407 ± 372</td>
<td>642 ± 712</td>
<td>2610 ± 1914</td>
</tr>
<tr>
<td>Acoustic parameters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$F_0$ (Hz)</td>
<td>392 ± 142</td>
<td>389 ± 136</td>
<td>194 ± 81</td>
</tr>
<tr>
<td>% Jitter</td>
<td>0.83 ± 0.83</td>
<td>1.10 ± 1.31</td>
<td>5.39 ± 2.76</td>
</tr>
<tr>
<td>% Shimmer</td>
<td>6.24 ± 7.04</td>
<td>6.30 ± 5.94</td>
<td>31.08 ± 15.49</td>
</tr>
<tr>
<td>SNR</td>
<td>18.14 ± 6.11</td>
<td>16.80 ± 7.04</td>
<td>4.27 ± 2.67</td>
</tr>
<tr>
<td>VKG parameters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ipsilateral amplitude (pixels)</td>
<td>4.48 ± 2.67</td>
<td>4.59 ± 2.75</td>
<td>4.97 ± 2.51</td>
</tr>
<tr>
<td>Contralateral amplitude (pixels)</td>
<td>5.70 ± 3.57</td>
<td>6.37 ± 3.45</td>
<td>3.88 ± 2.03</td>
</tr>
<tr>
<td>Intrafold phase difference</td>
<td>0.17 ± 2.24</td>
<td>-0.30 ± 0.24</td>
<td>-1.22 ± 2.95</td>
</tr>
<tr>
<td>Interfold phase difference</td>
<td>0.52 ± 2.89</td>
<td>0.20 ± 2.95</td>
<td>-0.54 ± 2.84</td>
</tr>
</tbody>
</table>

Table 2. Total classification accuracies (%) at each number of hidden nodes evaluated. Values are presented as mean ± standard deviation.

<table>
<thead>
<tr>
<th>Nodes</th>
<th>Normal</th>
<th>Tension asymmetry</th>
<th>Glottic insufficiency</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>84.02 ± 6.62</td>
<td>61.84 ± 15.22</td>
<td>98.2 ± 0.01</td>
<td>81.88 ± 3.26</td>
</tr>
<tr>
<td>40</td>
<td>85.20 ± 1.95</td>
<td>67.61 ± 11.38</td>
<td>98.11 ± 0.28</td>
<td>83.93 ± 3.02</td>
</tr>
<tr>
<td>60</td>
<td>84.87 ± 3.29</td>
<td>67.61 ± 6.33</td>
<td>97.93 ± 0.61</td>
<td>83.76 ± 2.94</td>
</tr>
<tr>
<td>80</td>
<td>83.07 ± 3.01</td>
<td>64.59 ± 9.34</td>
<td>97.47 ± 1.49</td>
<td>82.00 ± 2.41</td>
</tr>
<tr>
<td>100</td>
<td>84.48 ± 3.61</td>
<td>61.92 ± 13.60</td>
<td>97.75 ± 0.87</td>
<td>81.97 ± 3.37</td>
</tr>
<tr>
<td>120</td>
<td>80.56 ± 3.80</td>
<td>70.28 ± 8.28</td>
<td>97.56 ± 1.16</td>
<td>82.44 ± 2.91</td>
</tr>
<tr>
<td>140</td>
<td>83.24 ± 3.22</td>
<td>66.88 ± 10.13</td>
<td>97.75 ± 0.76</td>
<td>82.75 ± 2.70</td>
</tr>
<tr>
<td>160</td>
<td>80.50 ± 3.69</td>
<td>68.36 ± 8.06</td>
<td>97.84 ± 0.63</td>
<td>81.96 ± 2.40</td>
</tr>
<tr>
<td>180</td>
<td>83.58 ± 3.95</td>
<td>70.56 ± 5.78</td>
<td>98.11 ± 0.28</td>
<td>84.02 ± 1.90</td>
</tr>
<tr>
<td>200</td>
<td>81.85 ± 2.77</td>
<td>65.24 ± 11.91</td>
<td>98.11 ± 0.28</td>
<td>81.80 ± 3.53</td>
</tr>
</tbody>
</table>
Table 3. Summary classification accuracies for each category and group of parameters. Values are presented as mean ± standard deviation. Values are presented as mean ± standard deviation. VKG = videokymography.

<table>
<thead>
<tr>
<th>Parameter set</th>
<th>Normal</th>
<th>Tension asymmetry</th>
<th>Glottic insufficiency</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>All parameters</td>
<td>83.58 ± 3.95</td>
<td>70.56 ± 5.78</td>
<td>98.11 ± 0.28</td>
<td>84.02 ± 1.90</td>
</tr>
<tr>
<td>Aerodynamic</td>
<td>92.19 ± 4.57</td>
<td>19.31 ± 7.35</td>
<td>94.78 ± 0.89</td>
<td>74.33 ± 2.05</td>
</tr>
<tr>
<td>Acoustic</td>
<td>85.64 ± 5.35</td>
<td>28.38 ± 16.81</td>
<td>93.45 ± 2.02</td>
<td>73.25 ± 2.55</td>
</tr>
<tr>
<td>Videokymographic</td>
<td>85.04 ± 3.25</td>
<td>26.98 ± 9.11</td>
<td>63.91 ± 4.52</td>
<td>64.22 ± 2.26</td>
</tr>
<tr>
<td>Aero + Acoustic</td>
<td>89.89 ± 4.99</td>
<td>26.36 ± 12.13</td>
<td>98.92 ± 0.38</td>
<td>76.73 ± 2.08</td>
</tr>
<tr>
<td>Aero + VKG</td>
<td>92.01 ± 5.23</td>
<td>24.14 ± 17.66</td>
<td>96.92 ± 1.79</td>
<td>76.10 ± 3.47</td>
</tr>
<tr>
<td>Acoustic + VKG</td>
<td>86.81 ± 3.65</td>
<td>48.40 ± 7.83</td>
<td>93.98 ± 1.52</td>
<td>79.05 ± 7.49</td>
</tr>
</tbody>
</table>

Table 4. Classification rates for individual parameters. Values are presented as mean ± standard deviation. PTP = phonation threshold pressure; PTF = phonation threshold flow; PTW = phonation threshold power; F0 = fundamental frequency; SNR = signal-to-noise ratio; VKG = videokymography.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal</th>
<th>Tension asymmetry</th>
<th>Glottic insufficiency</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aerodynamic parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTP</td>
<td>73.18 ± 5.32</td>
<td>30.01 ± 13.18</td>
<td>47.65 ± 12.59</td>
<td>54.93 ± 4.39</td>
</tr>
<tr>
<td>PTF</td>
<td>91.22 ± 5.51</td>
<td>19.82 ± 16.16</td>
<td>94.41 ± 0.28</td>
<td>73.91 ± 2.02</td>
</tr>
<tr>
<td>PTW</td>
<td>86.55 ± 4.89</td>
<td>16.25 ± 7.31</td>
<td>78.27 ± 3.08</td>
<td>66.27 ± 1.56</td>
</tr>
<tr>
<td>Acoustic parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F0</td>
<td>68.37 ± 22.98</td>
<td>18.80 ± 11.27</td>
<td>81.53 ± 11.56</td>
<td>59.47 ± 9.73</td>
</tr>
<tr>
<td>% Jitter</td>
<td>88.65 ± 2.81</td>
<td>13.62 ± 5.89</td>
<td>83.54 ± 5.26</td>
<td>68.06 ± 1.40</td>
</tr>
<tr>
<td>% Shimmer</td>
<td>78.32 ± 5.71</td>
<td>24.96 ± 8.92</td>
<td>84.82 ± 5.48</td>
<td>66.53 ± 1.20</td>
</tr>
<tr>
<td>SNR</td>
<td>88.39 ± 5.04</td>
<td>16.97 ± 13.09</td>
<td>93.66 ± 3.01</td>
<td>71.65 ± 1.35</td>
</tr>
<tr>
<td>VKG parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ipsilateral amplitude</td>
<td>65.36 ± 23.35</td>
<td>22.33 ± 23.99</td>
<td>27.56 ± 14.74</td>
<td>43.66 ± 8.05</td>
</tr>
<tr>
<td>Contralateral amplitude</td>
<td>75.03 ± 5.17</td>
<td>20.80 ± 4.87</td>
<td>32.91 ± 9.69</td>
<td>49.26 ± 1.74</td>
</tr>
<tr>
<td>Intrafold phase difference</td>
<td>72.45 ± 12.49</td>
<td>22.01 ± 18.41</td>
<td>38.47 ± 9.91</td>
<td>49.94 ± 3.85</td>
</tr>
<tr>
<td>Interfold phase difference</td>
<td>80.91 ± 13.20</td>
<td>17.27 ± 8.56</td>
<td>38.00 ± 10.67</td>
<td>52.50 ± 4.66</td>
</tr>
</tbody>
</table>
REFERENCES


CHAPTER 7

Initial investigation of anterior approach to arytenoid adduction in excised larynges

Timothy M. McCulloch, Matthew R. Hoffman, Kieran E. McAvoy, and Jack J. Jiang

ABSTRACT

Hypothesis: Arytenoid adduction (AA) can dramatically improve voice quality in patients with vocal fold paralysis (VFP); however, it is technically challenging. We present an anterior approach to AA, where Gore-Tex suture attached to curled wire is passed through the thyroid cartilage or cricothyroid membrane via a guide needle and used to manipulate the muscular process of the arytenoid. Performing arytenoid adduction (AA) via an anterior approach leads to comparable aerodynamic and acoustic outcomes compared to traditional AA in an excised larynx model.

Study design: Repeated measures with each larynx serving as its own control.

Methods: We performed thyroplasty followed by traditional and anterior AA on excised larynges with simulated VFP. Aerodynamic and acoustic measurements were recorded.

Results: Anterior AA significantly improved aerodynamic (phonation threshold power: $p=0.003$) and acoustic parameters (percent jitter: $p=0.028$; percent shimmer: $p=0.001$; signal-to-noise ratio: $p=0.034$) compared to VFP in this excised larynx model. Anterior AA and traditional AA produced comparable improvements in all parameters (phonation threshold power: $p=0.256$; percent jitter: $p=0.616$; percent shimmer: $p=0.281$; signal-to-noise ratio: $p=0.970$).
Conclusions: Anterior AA is an alternative to traditional AA that is easier to perform and produces comparable improvements in laryngeal function.

INTRODUCTION

Arytenoid adduction (AA) was introduced by Isshiki et al. as an additional treatment for vocal fold paralysis (VFP), primarily indicated for patients with a wide glottal chink or bilateral superoinferior vocal fold asymmetry (Isshiki 1978). Sutures passed from the muscular process of the arytenoid through the thyroid cartilage can simulate the contractile forces of the lateral cricoarytenoid and thyroarytenoid muscles, medializing a paralyzed fold when tension is placed on the suture. Due to the cylindrical shape of the cricoarytenoid joint (Isshiki 1978), the vocal process moves downward during adduction and can correct a difference in the levels of the vocal folds by lowering the affected fold (Neuman 1994).

Though the procedure has shown great utility and can effectively decrease a wide posterior glottal gap, surgical success of the procedure is inconsistent (Inagi 2002). Determination of optimal adduction is based on empirical judgments made during intraoperative voicing, a subjective and potentially time-consuming method which does not consistently yield optimal results (Inagi 2002). Locating and manipulating the muscular process is also difficult, giving the procedure a high level of technical difficulty (Slavit 1992) and decreasing the frequency with which it is performed. Adduction arytenopexy was proposed as a new procedure designed to fix the arytenoid on the cricoid facet in a position conducive to optimal voice production (Zeitels 1998). While theoretically sound and potentially valuable, this procedure is not used as widely as AA.
When performed correctly, AA can produce dramatic improvement in laryngeal function. In a study retrospectively comparing patients undergoing medialization laryngoplasty (ML) and simultaneous ML-AA, patients undergoing ML-AA had significantly better vocal improvement as evaluated by the GRBAS rating scale and patient satisfaction (McCulloch 2000). ML is limited by an inability to close a wide posterior glottal chink and correct a difference in the horizontal plane of the vocal folds. This is due to the posterior glottis and arytenoids residing outside the paraglottic space affected by the thyroplasty implant (McCulloch 2000).

Exposing and manipulating the muscular process of the arytenoid remains challenging (Mahieu 1989; Woo 2000; Slavit 1994). Accordingly, recent attention has been paid to alternative approaches of performing AA. Hess proposed the sling arytenoid adduction, where a monofilament thread is slung around the muscular process of the arytenoid via an external approach (Hess 2011). This is a promising new method which was demonstrated to be effective in five excised larynges and two patients; however, there is potential for infection due to the endoluminal routing of the monofilament thread (Hess 2011) and it is unknown if the sling method can keep the arytenoid fixed over time. Friedrich et al. recently performed an anatomical study to determine if AA could be performed through a thyroplasty window (Friedrich 2012). They determined that the fovea oblonga near the muscular process may be a favorable point for fixation and manipulation by a surgical screw and can be accessed through the window.

We present an anterior approach to arytenoid adduction, where Gore-Tex suture attached to curled wire is passed through the thyroid cartilage or cricothyroid membrane via a guide needle and used to manipulate the muscular process of the arytenoid. We hypothesized that
performing arytenoid adduction (AA) via an anterior approach leads to comparable aerodynamic and acoustic voice outcomes compared to traditional AA in an excised larynx model.

MATERIALS AND METHODS

Larynges

Four larynges were excised postmortem from canines sacrificed for non-research purposes according to the protocol described by Jiang and Titze (Jiang 1993). As the properties of the canine and human larynx are similar (Noordzij 1998), it is an appropriate model for studying human laryngeal physiology. Larynges were examined for evidence of trauma or disorders; any larynges exhibiting trauma or disorders were excluded. Following visual inspection, larynges were frozen in 0.9% saline solution.

Apparatus

Prior to the experiment, the epiglottis, corniculate cartilages, cuneiform cartilages, and ventricular folds were dissected away to expose the true vocal folds. The superior cornu and posterosuperior part of the thyroid cartilage ipsilateral to the normal vocal fold were also dissected away to facilitate insertion of a lateral 3-pronged micrometer into the arytenoid cartilage. The larynx was mounted on the apparatus (figure 1) as specified by Jiang and Titze (Jiang 1993). A metal pull clamp was used to stabilize the trachea to a tube connected to a pseudolung which served as a constant pressure source.
Insertion of one 3-pronged micrometer in the arytenoid cartilage ipsilateral to the dissected thyroid cartilage allowed for adduction of one vocal fold, simulating unilateral VFP in the unadducted vocal fold as in Czerwonka et al. (Czerwonka 2009). An additional 3-pronged micrometer was placed against the contralateral thyroid lamina for stability without providing vocal fold adduction. Methodological consistency was maintained by always adducting the contralateral arytenoid (simulated normal) to the midline. Micrometer positioning remained constant across sets of trials within the same larynx. Tension on the vocal folds and control of vocal fold elongation was accomplished by attaching the superior anteromedial thyroid cartilage, just inferior to the thyroid notch, to an anterior micrometer. Vocal fold elongation and adduction remained constant for all trials.

The pseudolung used to initiate and sustain phonation in these trials was designed to simulate the human respiratory system. Pressurized airflow was passed through two Concha Therm III humidifiers (Fisher & Paykel Healthcare Inc., Laguna Hills, California) in series to humidify and warm the air. The potential for dehydration was further decreased by frequent application of 0.9% saline solution between trials. Airflow was controlled manually and was measured using an Omega airflow meter (model FMA-1601A, Omega Engineering Inc., Stamford, Connecticut). Pressure measurements were taken immediately before the air passed into the larynx using a Heise digital pressure meter (901 series, Ashcroft Inc., Stratford, Connecticut).

Acoustic data were collected using a dbx microphone (model RTA-M, dbx Professional Products, Sandy, Utah) positioned at a 45° angle to the vocal folds. The microphone was placed 10 cm from the glottis to minimize acoustic noise produced by turbulent airflow. Acoustic
signals were subsequently amplified by a Symetrix preamplifier (model 302, Symetrix Inc., Mountlake Terrace, Washington). A National Instruments data acquisition board (model AT-MIO-16; National Instruments Corp, Austin, Texas) and customized LabVIEW 8.5 software were used to record airflow, pressure, and acoustic signals on a personal computer. Aerodynamic data were recorded at a sampling rate of 100 Hz and acoustic data at 40,000 Hz. Experiments were conducted in a triple-walled, sound-attenuated room to reduce background noise and stabilize humidity levels and temperature.

*Experimental Methods*

Trials were conducted as a sequence of 5 second periods of phonation, followed by 5 second periods of rest. Five trials were performed for each condition. During each trial, airflow passing through the larynx was increased gradually and consistently until the onset of phonation. Larynges were thoroughly hydrated with saline solution between trials and between sets of trials to eliminate any potentially confounding effects of dehydration.

ML was performed using a Silastic implant (Dow Corning Corporation, Midland, MI). The implant was inserted through a thyroplasty window approximately 6 x 11 mm in size in the thyroid cartilage ipsilateral to the paralyzed vocal fold. The same Silastic implant created for each larynx was used during ML, traditional AA, and anterior AA trials. After conducting the ML trials, the implant was removed to perform the AA (traditional or anterior). After the suture
was passed and the arytenoid properly positioned, the implant was returned to the larynx prior to collecting data for the AA trials. Traditional AA was performed after a set of trials was conducted analyzing the effect of ML. The procedure was performed according to the clinical descriptions by Isshiki (Isshiki 1978). One suture was passed with a needle from the muscular process of the arytenoid anteriorly through the paraglottic space through the thyroid cartilage just lateral to the anterior commissure and the second inferior to the cartilage was tightened to rotate the arytenoid and adduct the simulated paralyzed fold. The optimal degree of rotation was determined using real-time measurements of vocal efficiency (Hoffman 2011). Following each procedure, the arytenoid was restored to its original, lateral position to ensure that any potential perceived benefit of the next procedure would not actually be due to the arytenoid already being placed in a medialized position. Images demonstrating vocal fold position for the normal, vocal fold paralysis, traditional AA, and anterior AA trials are provided in figure 2. The anterior approach is described in detail below.

Anterior approach to arytenoid adduction

Stainless steel wire with diameter of 0.015” and length of approximately 5 cm was curled around a 20 gauge needle. A hook was formed at one end of the wire by bending it approximately 2 mm from the end. The specific dimensions of the wire hook are not critical and the length can easily be decreased once placed inside the larynx if necessary. Gore-Tex suture was threaded through the curled wire and

Figure 3. Procedural device used in this excised larynx experiment. Suture-wire complex used to manipulate the muscular process of the arytenoid. Gore-Tex suture is passed through a curled wire that has a hook at the end. The suture-wire complex and a 20-gauge guide needle are placed within a 14-gauge needle. The guide needle is used to locate the muscular process. Once it is located, the 14-gauge needle containing the suture-wire complex is advanced.
doubled back outside the curled portion proximal to the hook. In this experiment, CV-2 expanded polytetrafluoroethylene (Gore-Tex) suture was used, though the particular size is not important and can be varied across cases. Once the suture-wire complex is created, it is threaded through a 14-gauge needle. A 20-gauge needle serving as a guide needle is also threaded through the 14-gauge needle (figure 3). When performing the procedure, the guide needle and thus suture-wire complex can be passed either through the thyroplasty window or through the cricothyroid membrane. The appropriate vector of pull can be achieved using either method. To ensure the necessary forces are applied to the arytenoid, the sutures should be pulled anteromedially. If the thyroplasty window approach is used, the vector should approximate the medial aspect of the window. The guide needle is passed first and advanced to the muscular process of the arytenoid (figure 4). Once the muscular process is reached and confirmed by visualization of arytenoid movement with manipulation of the guide needle, the 14-gauge needle containing the suture-wire complex is passed over the guide needle. When the muscular process is reached, the suture-wire complex is pushed outside the 14-gauge needle. The 14-gauge needle can then be removed. Verification that the suture-wire complex has been secured on the tissue surrounding the muscular process is made prior to removing the guide needle. After removal of the guide needle, optimal degree of medialization is obtained by tightening the suture; the two ends are then tied external to the larynx and secured.

Data Analysis
Airflow and pressure at the phonation onset were recorded as the phonation threshold flow (PTF) and phonation threshold pressure (PTP), respectively. Phonation threshold power (PTW) is the product of these values. PTF, PTP, and PTW were determined manually using customized LabVIEW 8.5 software.

Measured acoustic parameters included fundamental frequency (F₀), signal-to-noise ratio (SNR), percent jitter, and percent shimmer. Acoustic signals were trimmed using GoldWave 5.1.2600.0 (GoldWave Inc., St. John’s, Canada) and analyzed using TF32 software (Madison, WI).

Statistical analysis

Paired t-tests were performed to determine: 1) if anterior AA led to improved voice quality compared to simulated VFP; 2) if anterior AA produced the same degree of improvement in voice quality compared to traditional AA; and 3) if anterior AA restored normal voice, as demonstrated by comparisons to simulated normal. If data did not meet assumptions for parametric testing, Wilcoxon-Mann-Whitney rank sum tests were performed. All tests were two-tailed with a significance level of α=0.05.

RESULTS
**Aerodynamics**

Compared to vocal fold paralysis (VFP), anterior AA led to significantly lower PTP (p=0.045), PTF (p=0.006), and PTW (p=0.003). Aerodynamic parameters for anterior AA did not differ significantly compared to those obtained for either normal or traditional AA (table 1; table 3).

**Acoustics**

Compared to VFP, anterior AA led to significant decreases in percent jitter (p=0.028) and percent shimmer (p=0.001) and a significant increase in SNR (p=0.034). F0 was not significantly affected (p=0.250). Acoustic parameters for anterior AA did not differ significantly compared to those obtained for either normal or traditional AA (table 2; table 3); however, the difference in F0 between traditional AA and anterior AA approached significance (p=0.094).

**DISCUSSION**

We present and evaluate a new method of performing arytenoid adduction (AA). Rather than approaching the muscular process of the arytenoid posteriorly, Gore-Tex suture is attached to a curled wire and passed through the thyroid cartilage or cricothyroid membrane via a guide needle and used to manipulate the muscular process of the arytenoid. This method was shown to be feasible and effective in excised larynges and also demonstrated to produce results comparable to those obtained with traditional AA.

Ex vivo canine larynges have been used extensively to study vocal fold paralysis (Inagi 2002; Czerwonka 2009; Noordzij 1998). There are several anatomical differences in the canine larynx compared to the human, including more angulated thyroid and cricoid cartilages, and the
absence of a well-defined vocal ligament (Noordzij 1998). These differences did not affect the procedures performed in this study. Excised larynx experiments offer a valuable tool to evaluate and refine new phonosurgical procedures. Results can be obtained from the same larynx for a variety of conditions or treatments. Using excised larynges for this study allowed us to refine the method of muscular process manipulation. We were also able to make intra-larynx comparisons between anterior AA and VFP to confirm the treatment was effective, between anterior AA and traditional AA to confirm that the treatment is as effective as the current gold standard, and between anterior AA and normal to determine if the procedure restored normal voice. It is important to note that comparisons to simulated VFP in this study do not allow for the natural reinnervation which occurs in living organisms. This is a preliminary study exploring and demonstrating methodological feasibility and efficacy. After our equipment and technique are refined, we will apply the procedure to human patients to determine true effectiveness and also long-term stability.

This method is similar to that recently proposed by Friedrich et al. (Friedrich 2012); however, we use a hooked wire rather than a screw. As the hooked wire does not have to attach specifically to the muscular process of the arytenoid but rather can attach to any of the soft tissues surrounding it, it may be easier than a screw to insert. It is important to note that our experiment only measured immediate changes in vocal function in excised larynges and longer studies in living organisms are required to confirm that the suture-wire complex remains stably inside the larynx and provides long-lasting vocal fold medialization.

We have provided objective evidence using quantitative aerodynamic and acoustic parameters confirming that this method improves laryngeal function to roughly the same degree
as traditional AA. Though the outcomes achieved in this preliminary study were encouraging, several aspects of the procedure will be reviewed and may be modified in the future. First, the optimal size and shape of the wire and hook will be evaluated. The conformations used in this study were effective, but a differently sized or shaped hook may be necessary when placing the device inside the human larynx and requiring stability for an extended period of time. Secondly, we may wish to modify the method by which the sutures are secured at the end of the procedure, particularly if the device is inserted through the cricothyroid membrane. This tissue is less conducive to standard knot tying compared to cartilage and may benefit from a modified method of securement. One potential method would be to pass the sutures through holes in a microplate which then rests on the membrane. The two ends of the suture could be tied to secure the suture and the plate. Lastly, the technique was demonstrated in a small sample size. Four larynges were sufficient to demonstrate the principle and feasibility of the technique. The hypothesized trend was observed, as anterior AA produced functional outcomes similar to those produced by traditional AA. Phonation threshold pressure and power appeared lower (reflective of more efficient voice production) in anterior AA, while phonation threshold flow was approximately equal between the two treatments. Percent jitter and signal-to-noise ratio were approximately equal between the two treatments, while percent shimmer was higher in anterior AA (reflective of greater perturbation in cycle-to-cycle amplitude). Fundamental frequency was discernibly lower for traditional AA compared to anterior AA, though this difference did not reach statistical significance (p=0.094). While both were lower than the normal condition, as has been observed previously in clinical and basic science investigations (Hoffman 2011; Hoffman 2010; Su 2002), it is not readily clear why there was an apparent difference between the two methods of AA. This
issue will be the subject of future investigations. While no differences between the two treatments were statistically significant, the absence of evidence is not evidence of absence. Evaluating changes in acoustic and aerodynamic parameters in a larger sample with equivalence testing may be warranted. Refinements to anterior AA may also improve acoustic outcomes. Specifically, only one suture-wire complex was used to rotate the muscular process and achieve vocal fold medialization, while two sutures are typically passed when performing traditional AA. Follow-up experiments will determine if passing a second suture-wire complex provides additional stabilization and medialization.

As the method is refined, the benefits of it will be maintained. Notably, there were no statistically significant differences in aerodynamic or acoustic parameters between anterior AA and traditional AA (table 3). Though traditional AA can be challenging to perform (Inagi 2002), it is an effective procedure (McCulloch 2000). The added morbidity associated with traditional AA is primarily due to difficulty locating and manipulating the muscular process of the arytenoid. If this aspect of the procedure can be eliminated while maintaining the dramatic improvements in vocal function that AA can provide, it would be beneficial to both the surgeon performing the procedure as well as the patients experiencing its benefits.

A few changes would be made prior to using this approach in human patients (figure 5). First, a localizing trocar with a light fiber could be added to allow for visualization of the
muscular process during the procedure. Second, a protective guard could be added to cover the 14-gauge needle to ensure it does not advance until the muscular process has been reached. Third, simultaneous transnasal fiberoptic endoscopy and intraoperative voicing would be performed to evaluate vocal fold position and laryngeal function.

This method can be performed through either a thyroplasty window or the cricothyroid membrane. Approaching the muscular process via the cricothyroid membrane could potentially transform AA from a technically challenging and highly invasive operation performed in the operating room to a minimally invasive procedure performed in a minor procedure room. If a thyroplasty has not already been done and there is atrophy of the thyroarytenoid muscle, however, it would be best to perform the procedure in the operating room in conjunction with a medialization thyroplasty.

CONCLUSION

A novel approach to arytenoid adduction is presented. Objective, quantitative evidence from preliminary excised larynx experiments provide support for this technique that could eliminate the main technical challenges while maintaining the benefits of traditional arytenoid adduction. Modifications required to perform this procedure in human patients will be evaluated in future studies.

TABLES

Table 1. Summary aerodynamic data presented as mean ± standard deviation (n=4). A significance level of $\alpha=0.05$ was used for all tests. PTF = phonation threshold flow (L/min); PTP = phonation threshold pressure (cmH$_2$O); PTW = phonation threshold power (L/min * cmH$_2$O);
VFP = vocal fold paralysis; ML = medialization laryngoplasty; AA = arytenoid adduction. Values are presented as mean ± standard deviation.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal</th>
<th>VFP</th>
<th>ML</th>
<th>Traditional AA</th>
<th>Anterior AA</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTF</td>
<td>30 ± 11</td>
<td>106 ± 22</td>
<td>82 ± 17</td>
<td>47 ± 32</td>
<td>36 ± 21</td>
</tr>
<tr>
<td>PTW</td>
<td>693 ± 568</td>
<td>2414 ± 735</td>
<td>1614 ± 391</td>
<td>972 ± 1091</td>
<td>589± 616</td>
</tr>
</tbody>
</table>

Table 2. Summary acoustic data presented as mean ± standard deviation (n=4). A significance level of α = 0.05 was used for all tests. SNR = signal-to-noise ratio; F₀ = fundamental frequency; VFP = vocal fold paralysis; ML = medialization laryngoplasty; AA = arytenoid adduction. Values are presented as mean ± standard deviation.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal</th>
<th>VFP</th>
<th>ML</th>
<th>Traditional AA</th>
<th>Anterior AA</th>
</tr>
</thead>
<tbody>
<tr>
<td>F₀</td>
<td>390 ± 127</td>
<td>213 ± 48</td>
<td>220 ± 52</td>
<td>168 ± 47</td>
<td>285 ± 62</td>
</tr>
<tr>
<td>% Jitter</td>
<td>1.52 ± 1.15</td>
<td>5.33 ± 2.73</td>
<td>3.03 ± 0.53</td>
<td>1.49 ± 0.54</td>
<td>1.74 ± 0.98</td>
</tr>
<tr>
<td>% Shimmer</td>
<td>8.88 ± 6.29</td>
<td>28.75 ± 10.48</td>
<td>18.91 ± 4.30</td>
<td>5.58 ± 1.42</td>
<td>11.77 ± 9.03</td>
</tr>
<tr>
<td>SNR</td>
<td>17.37 ± 11.02</td>
<td>4.04 ± 3.49</td>
<td>5.65 ± 2.40</td>
<td>14.56 ± 3.85</td>
<td>14.40 ± 8.44</td>
</tr>
</tbody>
</table>

Table 3. P-values obtained from paired t-tests comparing the aerodynamic and acoustic outcomes obtained using anterior arytenoid adduction to those obtained from the other conditions.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal</th>
<th>VFP</th>
<th>ML</th>
<th>Traditional AA</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTP</td>
<td>0.150</td>
<td>0.045</td>
<td>0.072</td>
<td>1.000</td>
</tr>
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<td>PTF</td>
<td>0.498</td>
<td>0.006</td>
<td>&lt;0.001</td>
<td>0.410</td>
</tr>
<tr>
<td>PTW</td>
<td>0.620</td>
<td>0.003</td>
<td>0.001</td>
<td>0.256</td>
</tr>
<tr>
<td>F₀</td>
<td>0.340</td>
<td>0.250</td>
<td>0.303</td>
<td>0.094</td>
</tr>
<tr>
<td>% Jitter</td>
<td>0.340</td>
<td>0.028</td>
<td>0.079</td>
<td>0.616</td>
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<tr>
<td>% Shimmer</td>
<td>0.748</td>
<td>0.001</td>
<td>0.253</td>
<td>0.281</td>
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<tr>
<td>SNR</td>
<td>0.357</td>
<td>0.034</td>
<td>0.083</td>
<td>0.970</td>
</tr>
</tbody>
</table>

REFERENCES


CHAPTER 8

Excised larynx evaluation of wedge-shaped adjustable balloon implant for minimally invasive type I thyroplasty

Matthew R. Hoffman, Erin E. Devine, Timothy M. McCulloch, and Jack J. Jiang

ABSTRACT

Objective: To describe the method by which the wedge-shaped adjustable balloon implant (wABI) can be inserted via a minithyrotomy for medialization thyroplasty and evaluate its effect on a range of phonatory parameters using the excised larynx bench apparatus.

Study design: Repeated measures with each larynx serving as its own control.

Methods: Medialization thyroplasty (MT) with the wABI was performed on six excised canine larynges. Mucosal wave, aerodynamic, and acoustic parameters were measured for three conditions: normal; vocal fold paralysis; and paralysis with the wABI.

Results: Phonation threshold pressure (p<0.001), flow (p<0.001), and power (p=0.002) were significantly lower for wABI compared to paralysis trials; values did not differ significantly from normal trials. Percent jitter (p=0.002) and percent shimmer (p=0.007) were also significantly decreased compared to the paralysis condition, and values were not significantly different compared to normal. The mucosal wave was preserved after insertion of the wABI.

Conclusions: Effective vocal fold medialization with preservation of the mucosal wave was observed with the wABI in this preliminary excised larynx experiment. The wABI offers the potential for a minimally invasive insertion in addition to postoperative adjustability. Further studies in living animals and humans are warranted to evaluate the clinical utility of this implant.
INTRODUCTION

Imperfect glottal closure is the primary etiology of dysphonia (Isshiki 1998), preventing efficient transduction of aerodynamic energy into acoustic energy and leading to a breathy, hoarse voice (Crumley 1994). Numerous studies have addressed this important clinical issue, beginning with the initial descriptions of paraffin injection by Brunings (Brunings 1911) and the use of a pedicled thyroid cartilage flap by Payr (Payr 1915), and continuing with the more detailed descriptions of medialization thyroplasty (MT) by Isshiki (Isshiki 1974) and Koufman (Koufman 1986). Since these foundational studies, a variety of implants have been proposed, each offering potential benefits and capable of significantly improving patient voice if used correctly. While currently used implants such as the titanium vocal fold medializing implant (TVFMI) (Friedrich 1999) and expanded polytetrafluoroethylene (McCulloch 1998) represent valuable advances in the management of glottic insufficiency, both are inserted via the standard thyroplasty operation and require a revision thyroplasty for any postoperative modifications other than supplementary vocal fold injection.

Reported revision rates have varied across studies. Rosen reported a relatively low rate of 5.5% based on responses to a national survey (Rosen 1998) and Koufman reported a rate of 12.5% in a series of 56 patients (Koufman 1991). In a retrospective review of 96 patients, Anderson et al. reported that 33% underwent secondary surgical procedures (Anderson 2003). This higher revision rate may be in part attributed to a high portion of patients being professional voice users, including professional singers in whom secondary procedures were performed more frequently. While MT has been traditionally performed for unilateral vocal fold paralysis, it can also be performed for other causes of glottic insufficiency, such as paresis, atrophy, bowing,
scarring, and presbylaryngis. If performed in a patient with a progressive disorder such as presbylaryngis, future revisions can be anticipated as the previous degree of medialization is no longer sufficient to achieve vocal fold approximation (Woo 2001).

In a previous study, we presented the adjustable balloon implant (ABI) for MT (Hoffman 2011). A spherical silicone balloon was introduced into excised larynges, stabilized with a metal frame, and filled with saline until the desired degree of medialization was achieved. This implant had the key potential advantage of allowing for minimally invasive revisions. Though promising, insertion was still performed via a traditional thyroplasty window and the spherical shape required placement of a frame with superior and inferior flanges to ensure the primary force vector was directed medially.

To address these issues, we considered modifying the shape of the implant to allow for a less invasive insertion as well as alleviate concerns regarding balloon shape once fully inflated. Here, we present a wedge-shaped adjustable balloon implant (wABI) which can be inserted via a minithyrotomy and does not require a supporting frame. Additionally, the wedge shape may allow for closure of a posterior glottal chink which was not possible with a spherical implant. The purposes of this preliminary excised larynx study were to determine if the wABI could be used effectively for vocal fold medialization, determine if insertion of the wABI could restore normal phonation, and to verify that insertion of the wABI did not eliminate the mucosal wave.

MATERIALS AND METHODS

Larynges. Six larynges were excised postmortem from canines sacrificed for unrelated purposes according to the protocol described by Jiang and Titze (Jiang 1993). Canine larynges
have been used extensively to study laryngeal physiology including vocal fold paralysis (Noordzij 1998; Czerwonka 2009; de Souza Kruschewsky 2007). Following visual inspection to ensure no signs of trauma or disorders were present, larynges were frozen in 0.9% saline.

**Apparatus.** Prior to the experiment, the epiglottis, corniculate and cuneiform cartilages, and ventricular folds were removed to allow for imaging of vocal fold vibration. The superior cornu and posterosuperior part of the thyroid cartilage were also removed to facilitate insertion of a lateral 3-pronged manipulator into the arytenoid cartilage. The larynx was mounted on the apparatus (figure 1) as specified by Jiang and Titze (Jiang 1993). A metal hose clamp secured the trachea to a tube connected to a pseudolung which served as a constant pressure source. Pressurized airflow was passed through two humidifiers (Fisher & Paykel Healthcare Inc., Laguna Hills, California) to humidify and warm the air. Airflow was controlled manually and measured using an Omega airflow meter (model FMA-1601A, Omega Engineering Inc., Stamford, Connecticut). Subglottal pressure was recorded using a pressure transducer (Series 3850A, Hans Rudolph, Inc., Kansas City, MO).

Acoustic data were collected using a dbx microphone (model RTA-M, dbx Professional Products, Sandy, Utah) positioned at a 45° angle to the vocal folds, approximately 10 cm from the glottis to minimize acoustic noise produced by turbulent airflow when simulating vocal fold paralysis. Acoustic signals were amplified by a Symetrix preamplifier (model 302, Symetrix Inc.,
Mountlake Terrace, Washington). A National Instruments data acquisition board (model AT-MIO-16; National Instruments Corp, Austin, Texas) and customized LabVIEW 8.5 software were used to record airflow, pressure, and acoustic signals on a computer. Aerodynamic data were sampled at 100 Hz and acoustic data at 40,000 Hz. Experiments were conducted in a triple-walled, sound-attenuated room to stabilize humidity and reduce background noise.

Vocal fold vibration was recorded for approximately 200 milliseconds per trial using a high-speed digital camera (model Fastcam-ultima APX; Photron, San Diego, CA). Videos were recorded with a resolution of 512 x 256 pixels at a rate of 4000 frames/second.

Figure 2. Wedge-shaped adjustable balloon implant with three degrees of inflation: empty (left); filled to appropriate volume (middle); and overfilled (right). Far right shows position of implant within larynx.

Wedge-shaped adjustable balloon implant. The implant (figure 2) was manufactured by Hood Laboratories (Pembroke, MA) based on the authors’ design. The balloon is wedge-shaped with a triangular base comprised of legs that are 15 and 8 mm in length and a height of 6 mm. Dimensions were determined based on measurements of a variety of excised larynges and designed to be big enough to allow for medialization of larger larynges while still small enough to be folded and passed through an anterior minithyrotomy. The implant has a wall thickness of
0.15 mm and is connected via tubing with outside diameter of 1.5 mm to a luer slip one-way check valve. Both the balloon and tubing were made using 50 durometer medical grade silicone.

The implant was inserted via a minithyrotomy approach. A small opening, approximately 3 mm × 3 mm in size, was created in the thyroid cartilage, 2-3 mm lateral of the midline. The opening could be either circular and created by a drill or rectangular and created by a scalpel; both methods were employed in this study with no difference in effectiveness. The level of the opening was created midway between the thyroid notch and inferior margin of the thyroid cartilage, which was presumed to be the level of the vocal fold. Prior to inserting the implant, a probe was passed through the opening and along the interior margin of the thyroid cartilage to expand the space lateral to the thyroarytenoid muscle where the implant would eventually reside. The implant was empty at the time of insertion and the rectangular base was folded to further decrease the size of the implant as it was inserted. When passing the implant through the opening, it could either simply be pushed through gently or passed while holding the proximal end with a forceps. Once inside, the implant was filled to the desired volume until approximation to the contralateral fold was achieved. Further minor adjustments were made based on real-time measurements of aerodynamic (pressure and airflow) and acoustic (percent jitter, percent shimmer) parameters. Expanding the implant within the larynx ensures it will not fall out, as the implant is now significantly larger than the opening through which it was passed; a stitch could be placed around the tube and opening if desired, though was not done in this study. The same implant was used for all larynges, which varied slightly in size.

**Experimental methods.** Five trials were performed for each of three conditions: normal; unilateral vocal fold paralysis (VFP); and paralysis with the wABI inserted and filled to an
optimal volume. Trials were conducted as a sequence of 5 seconds of phonation followed by 5 seconds of rest. To simulate normal, both arytenoids were adducted with lateral prongs. To simulate VFP, only the right arytenoid was adducted to the midline; the left was not adducted. This same setup was used for the wABI condition, but the implant was inserted and filled. Control of vocal fold elongation was accomplished by connecting the thyroid cartilage, just inferior to the thyroid notch, to an anterior micrometer. Vocal fold elongation and contralateral adduction remained constant across trials within each larynx. During each trial, airflow was increased gradually until stable phonation was achieved. Larynges were thoroughly hydrated with 0.9% saline solution between trials to prevent dehydration.

**Data analysis.** Phonation was evaluated in three conditions: normal; simulated VFP; and VFP with the wABI. Airflow and pressure at the phonation onset were recorded as the phonation threshold flow (PTF) and phonation threshold pressure (PTP), respectively. Phonation threshold power (PTW) was calculated as the product of these values.

Measured acoustic parameters included signal-to-noise ratio (SNR), percent jitter, and percent shimmer. Acoustic signals were trimmed to produce three 1-second segments per trial using GoldWave 5.1.2600.0 software (GoldWave Inc., St. John’s, Canada) and these segments were analyzed using TF32 software (Madison, WI).

High-speed video recordings of vocal fold vibration were analyzed using a customized MATLAB program (The MathWorks, Natick, MA). Vibratory properties of each of the four vocal fold lips (right upper, right lower, left upper, and left lower) were quantified via digital videokymography (VKG). Threshold-based edge detection, manual wave segment extraction, and nonlinear least squares curve fitting using the Fourier Series equation were applied to
determine the most closely fitting sinusoidal curve. This curve was then used to derive the amplitude and phase difference of the mucosal wave of each vocal fold lip. Mucosal wave amplitude was measured for each vocal fold and calculated as the average of the amplitudes of the upper and lower lips. Three parameters of interest relevant to this investigation included: interfold phase difference, which is reflective of vibrational phase symmetry between the two vocal folds; difference between right and left mucosal wave amplitudes, which was measured to confirm that vibrational amplitude symmetry was not lost due to implant insertion; and left vocal fold amplitude after insertion of the wABI, to confirm inserting the implant did not eliminate the mucosal wave. Interfold phase difference was determined using the method described by Krausert et al. (Krausert 2011), where a phase difference of \( \pi \) radians represents perfectly symmetric vibration, and a phase difference of zero radians represents perfectly asymmetric vibration.

**Statistical analysis.** Paired t-tests were performed to determine if significant differences occurred between paired conditions of interest (normal and VFP, to confirm that simulation of paralysis significantly affected voice production; VFP and wABI, to confirm that insertion of the wABI significantly improved voice production; and normal and wABI, to determine if insertion of the wABI restored voice to its normal state). Individual paired t-tests rather than a comprehensive analysis of variance were performed as the pairwise comparisons were of greater experimental interest. If data did not meet
assumptions of parametric testing, a Wilcoxon-Mann-Whitney rank sum test was performed. Tests were two-tailed with a significance level of \( \alpha = 0.05 \). To confirm that insertion of the wABI did not eliminate the mucosal wave, a one-sample t-test was performed on the left vocal fold vibratory amplitude data with the null hypothesis that amplitude was equal to zero.

**RESULTS**

Summary data are presented in table 1.

**Aerodynamics.** Inserting the wABI significantly decreased PTP (\( p < 0.001 \)), PTF (\( p < 0.001 \)), and PTW (\( p = 0.002 \)) relative to VFP (table 2; figure 3). There were no significant differences in aerodynamic parameters between the normal and wABI conditions.

**Acoustics.** The wABI significantly increased SNR (\( p = 0.002 \)) and significantly decreased percent jitter (\( p = 0.002 \)) and percent shimmer (\( p = 0.007 \)) relative to VFP (table 2; figure 4). There were no significant differences in acoustic parameters between the normal and wABI conditions.

**Mucosal wave.** Interfold phase difference was not significantly different between any of the pairs (table 2). The absolute difference between right and left vibratory amplitude was also not different (table 2). Left vocal fold vibratory amplitude for wABI trials was significantly greater than zero (\( p < 0.001 \)).
DISCUSSION

The wABI, a modified version of the adjustable balloon implant (Hoffman 2011), provided effective medialization in our preliminary excised larynx experiment. The focused modifications appeared to have simplified implant insertion and led to improved outcomes.

Adequate medialization was achieved in all larynges, as demonstrated by restoration of aerodynamic parameters to near normal levels. This represents a key improvement over our previous implant design. A spherical shape did not allow for closure of the posterior glottis, leading to values of phonation threshold flow which were less than that for VFP, but greater than normal. Using a wedge shape effectively closed the posterior gap and reduced air leakage through the posterior glottis. In female patients, such a posterior gap may be desirable, in which case a sphere or modified wedge with an angled posteromedial aspect could be used.

Significant improvements were observed in all acoustic parameters. Decreased percent jitter and shimmer can be attributed to restored vibrational periodicity, while an increase in the SNR was due to decreased airflow and increased acoustic amplitude. It is important to note that perturbation parameters were slightly
higher in the wABI condition compared to normal (table 1). While these differences were not significant and values were within the range for a type 1 voice signal, more detailed intraprocedural acoustic monitoring or further implant refinements could be employed to ensure levels return to normal.

When placing an implant in the larynx, there is potential for placing pressure on the superficial lamina propria and disrupting the normal mucosal wave if the implant is too large. Filling the implant with an excessive amount of saline could cause bulging and eliminate normal vibration for that vocal fold. Stable phonation could still occur provided vocal fold approximation is achieved, as demonstrated in a hemilarynx experiment (Jiang 1993); however, this situation is clinically suboptimal. To ensure that insertion of the wABI did not cause these adverse effects, we evaluated ipsilateral mucosal wave amplitude using a one-sample t-test. Comparisons across conditions could be performed, but would be confounded by different input pressures, as subglottal pressure is related to mucosal wave amplitude (Jiang 2008), and phonation threshold pressure for VFP trials may exceed phonation instability pressure for normal or implant trials. Testing confirmed that the mucosal wave was preserved after implant insertion (figure 6). Additionally, the difference between right and left vibratory amplitude, a measure of vibrational symmetry, was also determined. This measurement is relative and more immune to the aforementioned dependence on subglottal pressure. These tests revealed no significant differences across conditions, though the wABI trials did have the overall largest value. It may be beneficial to investigate the effects of inserting a smaller implant between the thyroid cartilage and inner perichondrium, which would provide medialization while not potentially affecting the mucosal wave. Using the appropriate amount of saline could also be sufficient.
It is important to acknowledge several limitations which will be the focus of future investigations. First and foremost, this is a preliminary study using excised canine larynges. While this is sufficient to evaluate the ability of the implant to medialize a vocal fold, we were unable to evaluate long-term stability or local tissue response. Second, a relatively modest sample size was included. The significant differences between the wABI and VFP conditions are not likely to change; however, some differences between the wABI and normal conditions may become statistically significant with a larger sample. A relatively large base for the wedge shape was selected to ensure the same implant could be used for larynges of varying size. While this medialization was adequate, superior results may potentially be obtained by using different sized implants for different larynges. Lastly, it was not possible to record the vocal output for each condition at the same subglottal pressure. The high pressure needed for phonation in the VFP condition could cause chaotic vibration in the normal or wABI conditions. If a consistent input of approximately 10 cmH$_2$O were used, the vast majority of larynges simulating VFP would be aphonic, precluding quantitative comparisons.

As with our previous design, the chief advantage is the potential for postoperative adjustability without a revision thyroplasty, a feature not available with currently used implants. The adjustable laryngeal implant proposed by Dean et al. allows the surgeon to control the degree of medialization using a micrometric screw (Dean 2001); however, postoperative modification would require access to the screw, which could require a second operation. Not every patient would benefit from an
adjustable implant, and currently available implants can often produce results for which revisions are unnecessary. However, there are specific situations when the ability to perform minimally invasive postoperative adjustments would be valuable. For less experienced surgeons, the ability to revise a suboptimal result would be beneficial. Second, professional voice users, in whom high quality voice is critical to livelihood, may require multiple fine adjustments to ensure the best possible voice is achieved (Anderson 2003). Third, persons with progressive disorders such as presbylaryngis may require modifications as severity of their voice disorder increases (Woo 2001).

A key consideration when designing the implant was creating something which could eventually be inserted using only a minimally invasive procedure, potentially accomplished in a minor procedure room rather than an operating room. Insertion in this study required only a small opening (approximately 3 mm x 3 mm) in the thyroid cartilage (figure 7) and resulted in complete closure of the glottal gap (figure 6). While implant shape and method of insertion provide the possibility of a minimally invasive approach, initial human trials would naturally need to be conducted in the controlled setting of the operating room. Determining feasible implant insertion methods will be a key focus of future animal and human studies.

CONCLUSION

A wedge-shaped version of the adjustable balloon implant to be used in medialization thyroplasty is presented. This retains the key benefit of our original implant, namely postoperative adjustability, and also offers closure of the posterior glottal gap and a simpler method of insertion. Taking advantage of the wedge shape may mean that implants of different
size must be used for different patients, though a single implant was sufficient in our sample of six canine larynges. This study provides preliminary support for the biomechanical effects of the implant. Investigations evaluating implant insertion and postoperative adjustment in living animals will be the subject of future research once implant refinements are complete.

ACKNOWLEDGEMENTS

The authors thank Adam Rieves for his help creating the images presented in this paper. This study was funded by NIH grant numbers NIH grant numbers F31 DC012495 and R01 DC008153 from the National Institute on Deafness and other Communicative Disorders.

TABLES

Table 1. Summary aerodynamic, acoustic, and mucosal wave data. VFP = vocal fold paralysis; wABI = wedge-shaped adjustable balloon implant; PTF = phonation threshold flow; PTP = phonation threshold pressure; SNR = signal-to-noise ratio; PD = phase difference.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal</th>
<th>VFP</th>
<th>wABI</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTF (L/min)</td>
<td>18.5 ± 6.8</td>
<td>111.7 ± 17.9</td>
<td>21.0 ± 7.3</td>
</tr>
<tr>
<td>PTP (cmH$_2$O)</td>
<td>7.23 ± 2.49</td>
<td>18.57 ± 3.97</td>
<td>8.13 ± 3.65</td>
</tr>
<tr>
<td>PTW (cmH$_2$O*L/min)</td>
<td>124.6 ± 33.8</td>
<td>2120.6 ± 798.7</td>
<td>164.9 ± 94.6</td>
</tr>
<tr>
<td>SNR</td>
<td>16.74 ± 3.99</td>
<td>3.51 ± 2.08</td>
<td>13.67 ± 3.73</td>
</tr>
<tr>
<td>Percent jitter</td>
<td>0.51 ± 0.31</td>
<td>5.77 ± 2.08</td>
<td>0.79 ± 0.31</td>
</tr>
<tr>
<td>Percent shimmer</td>
<td>4.21 ± 2.43</td>
<td>26.90 ± 11.66</td>
<td>6.25 ± 1.70</td>
</tr>
<tr>
<td>Interfold PD (radians)</td>
<td>2.54 ± 0.38</td>
<td>2.55 ± 0.35</td>
<td>2.44 ± 0.29</td>
</tr>
<tr>
<td>R–L amplitude (pixels)</td>
<td>1.13 ± 0.88</td>
<td>0.85 ± 0.66</td>
<td>1.48 ± 1.66</td>
</tr>
</tbody>
</table>

Table 2. P-values obtained from paired t-tests between condition pairs. VFP = vocal fold paralysis; wABI = wedge-shaped adjustable balloon implant; PTF = phonation threshold flow;
PTP = phonation threshold pressure; SNR = signal-to-noise ratio; PD = phase difference. Asterisks indicate significant p-values.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal, VFP</th>
<th>VFP, wABI</th>
<th>Normal, wABI</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTP</td>
<td>&lt;0.001*</td>
<td>&lt;0.001*</td>
<td>0.184</td>
</tr>
<tr>
<td>PTF</td>
<td>&lt;0.001*</td>
<td>&lt;0.001*</td>
<td>0.844</td>
</tr>
<tr>
<td>PTW</td>
<td>0.031*</td>
<td>0.002*</td>
<td>0.438</td>
</tr>
<tr>
<td>SNR</td>
<td>0.002*</td>
<td>0.002*</td>
<td>0.349</td>
</tr>
<tr>
<td>Percent jitter</td>
<td>0.001*</td>
<td>0.002*</td>
<td>0.206</td>
</tr>
<tr>
<td>Percent shimmer</td>
<td>0.009*</td>
<td>0.007*</td>
<td>0.249</td>
</tr>
<tr>
<td>Interfold PD</td>
<td>0.947</td>
<td>0.312</td>
<td>0.552</td>
</tr>
<tr>
<td>R – L amplitude</td>
<td>0.530</td>
<td>0.310</td>
<td>0.564</td>
</tr>
</tbody>
</table>

REFERENCES


CHAPTER 9

Conclusion

A. INTRODUCTION TO DISCUSSION

This series of studies was designed to provide the foundation for a new set of devices capable of facilitating minimally invasive permanent vocal fold medialization. Voice disorders have a lifetime prevalence of 30% (Cohen 2012) with glottic insufficiency as the primary anatomic etiology (Isshiki 1998). The impact of glottic insufficiency on patient quality of life can be significant (Spector 2010). Accordingly, new research directed at improving the clinical care of these patients is warranted. In addition to describing new devices for vocal fold medialization, an experimental method and variety of parameters were also evaluated. Utilizing the advantages and addressing the limitations of the method and analyses will be important as this line of study is continued.

A.1 General conclusions

Several broad conclusions can be drawn from the series of seven studies. First, the excised larynx bench apparatus is suitable for evaluating the biomechanical effects of vocal fold medialization. Excised larynx experiments have played a key role in basic science research on vocal fold paralysis and the surgical treatments for it (Noordzij 1998; Czerwonka 2009). My series of studies provides additional support for its role in investigating this important problem. Importantly, both aerodynamic input and acoustic output can be evaluated in a single model. While no vocal tract is included, inclusion of a vocal tract would likely only change the
characteristics of the sound produced rather than the actual process of energy transduction which produces sound.

As predicted, a wide range of phonatory parameters were responsive to the degree of medialization. This was demonstrated most precisely in our study on optimizing arytenoid adduction using real-time quantitative voice parameters (Hoffman 2011). While vocal efficiency and perturbation parameters were targeted due to their potential use in an operating room, other parameters including mucosal wave amplitude and phonation threshold power also displayed similar trends, with local extrema occurring at the arytenoid position deemed optimal. The set of parameters used to evaluate medialization was also useful when performing pattern recognition to distinguish normal phonation from either glottic insufficiency or tension asymmetry (Hoffman 2012).

Third, the mechanical interventions of medialization thyroplasty and arytenoid adduction can be accomplished using a variety of methods. This has been observed previously with various investigators offering their particular derivation with which they have had success (Friedrich 1999; McCulloch 1998; Cummings 1993; Hess 2011; Friedrich 2012). We developed methods which could potentially decrease the invasiveness of these procedures, and found that even the less invasive methods produced phonatory outcomes which were similar to those achieved in the normal condition (Hoffman 2011; McCulloch 2013; Hoffman, under review).

These primary findings will be discussed in their clinical and scientific context. These particular contexts were selected as biomedical research should inform both our understanding of a clinical problem as well as our ability to treat it. Additionally, as these experiments were
conducted using excised larynges and intended to lay the foundation for future in vivo animal and clinical studies, future directions are discussed.

B. SUMMARY OF KEY FINDINGS

A brief summary of the findings from each study is presented. Following the individual study summaries, a comprehensive table outlining key points and how findings filled gaps in knowledge is provided.

B.1 Multi-parameter analysis of injection laryngoplasty, medialization laryngoplasty, and arytenoid adduction in an excised larynx model

Unilateral vocal fold paralysis was simulated in sixteen excised canine larynges. Aerodynamic, acoustic, and mucosal wave measurements were obtained for eight larynges before and after injection laryngoplasty using micronized dermis and for a second set of eight larynges before and after medialization thyroplasty with a Silastic implant and then again after arytenoid adduction. Injection and thyroplasty led to comparable voice improvements, with the only notable difference being decreased mucosal wave amplitude following injection. Combined thyroplasty-arytenoid adduction led to the greatest improvement in all parameters.

Most of these findings were expected and served to provide objective evidence that comparable temporary improvements can be obtained with either injection or thyroplasty and that adding arytenoid adduction to thyroplasty has value. One finding was unexpected and a second served as the motivation for study B.3. Decreased mucosal wave amplitude was observed in the set of larynges undergoing injection. This could be due to one of two things. First, the injection could have been performed incorrectly with the injectate directly impinging on the
lamina propria rather than staying within or lateral to the thyroarytenoid muscle. Second, there
could have been effects on vibration even though the injectate remained lateral to the lamina
propria. This has been observed by Mau et al. (2012) in excised larynges as well as by Anderson
and Sataloff clinically (Anderson 2004). A similar phenomenon was observed by Gardner and
Parnes after Teflon injection (Gardner 1991). We did not perform a detailed histological analysis
and thus could not determine which scenario occurred, but possible global effects due to local
injection warrant further investigation. Second, it was observed that three of the eight larynges
had a worse arytenoid adduction outcome with a larger residual glottal gap and higher
perturbation. This provided motivation to conduct the study using real-time monitoring of
phonatory parameters to confirm the arytenoid had been rotated to a sufficient degree.

B.2 Multiparameter analysis of titanium vocal fold medializing implant in an excised
larynx model

Unilateral vocal fold paralysis was simulated in eight excised canine larynges and
aerodynamic, acoustic, and videokymographic measurements were obtained before and after
medialization with the titanium vocal fold medializing implant. This study was conducted in
collaboration with the inventor of this implant, Dr. Gerhard Friedrich (Friedrich 1999). Similar
trends were observed in this as in the other studies included in this series. Namely, significant
decreases in threshold aerodynamics and perturbation parameters with a significant increase in
signal-to-noise ratio were observed. Specific to this study, I found the titanium vocal fold
medializing implant easier to use than the Silastic implant. The adjustable posterior flange allows
for significant medialization as well as application to larynges of varying size, while the
anchoring sutures provide excellent stability.
B.3 Optimal arytenoid adduction based on quantitative real-time voice analysis

We determined how vocal efficiency and perturbation parameters (percent jitter and percent shimmer) changed while rotating the arytenoid during arytenoid adduction. The “optimal” arytenoid position was that which coincided with maximal vocal efficiency and minimal perturbation. Once this point was found, the arytenoid was hypo- and hyper-rotated approximately 10 degrees to determine how vocal fold hypo- and hyper-adduction affected phonatory parameters. Six experimental conditions were evaluated: normal; simulated unilateral paralysis; thyroplasty; optimal arytenoid adduction; hypo-rotated arytenoid adduction; and hyper-rotated arytenoid adduction.

Across the five larynges, optimal angle of arytenoid adduction (angle formed by the membranous vocal fold and medial edge of arytenoid) was rather consistent with an average position of 151.4±2.5 degrees. Importantly, changes in vocal efficiency and perturbation parameters coincided and were as expected. A similar pattern of variation was also observed for phonation threshold pressure, flow, and power as well as mucosal wave amplitude. The main goal of this experiment was not to demonstrate that parameters were significantly different with the arytenoid in the optimal position compared to the hypo- or hyper-rotated positions; rather, it was to determine how parameters changed as the arytenoid was rotated. With the small change in rotation of ±10 degrees, significantly different outcomes were not expected. However, parameters did tend to change noticeably in a predictive fashion. This method has potential promise for use clinically, as the parameters would be relatively easy to measure intraoperatively. However, it would be important to proceed with some degree of caution as
optimal position for voice could potentially be slightly adducted past midline which could have adverse effects on respiration.

**B.4 Preliminary investigation of adjustable balloon implant for type I thyroplasty**

This experiment was the culmination of over two years of proposed ideas, revised ideas, and discussions among the four authors as well as with the company which manufactured the first prototype, Hood Laboratories. The motivation for the study was to create a thyroplasty implant which could be easily adjusted postoperatively and could also accommodate a variety of larynges. This specific experiment was conducted to present the concept and demonstrate that the end result, a spherical inflatable silicone balloon with stabilizing metal frame, could be used to achieve vocal fold medialization.

Three conditions were evaluated in five excised canine larynges: normal; simulated unilateral paralysis; and thyroplasty with the adjustable balloon implant. Key findings included significant decreases in threshold aerodynamic as well as perturbation parameters with the implant compared to the paralysis condition. Importantly, the mucosal wave was preserved after implant insertion, obviating potential concerns that the implant could be over-inflated and press against the lamina propria. While the adjustable balloon implant was effective at medializing the vocal fold, the spherical shape resulted in a residual posterior glottic gap with significantly higher phonation threshold flow and power compared to normal trials. This finding served as part of the motivation for study B.7, as a wedge-shaped balloon may be better able to close a posterior gap.

**B.5 Classification of glottic insufficiency and tension asymmetry using a multilayer perceptron**
This study was conducted to demonstrate the value of multiparameter voice analysis. Aerodynamic, acoustic, and videokymographic data were collected for excised larynges in three conditions: normal; tension asymmetry (simulated superior laryngeal nerve paralysis); and glottic insufficiency (simulated recurrent laryngeal nerve paralysis). Varying severities of tension asymmetry and glottic insufficiency were included. A multilayer perceptron artificial neural network was used to classify data into the three groups based on values of the phonatory parameters. When including all parameters, 84% of data were classified correctly. Including only aerodynamic or acoustic parameters produced classification rates of approximately 75% while including only videokymographic parameters produced classification rates of approximately 65%. Most incorrect classifications occurred when identifying normal or tension asymmetry trials, as the two produced similar phonatory parameter profiles. Several conclusions can be drawn from this preliminary study. First, a comprehensive voice assessment likely has value over isolated measurements analyzing one aspect of the voice production mechanism. Second, more sophisticated acoustic and videokymographic measurements are required to identify the subtle abnormalities associated with tension asymmetry. In a separate study, we demonstrated that the nonlinear dynamic parameter second-order entropy was significantly different between symmetric and asymmetric tension trials (Devine 2012) and may be useful in that regard.

B.6 Initial investigation of anterior approach to arytenoid adduction in excised larynges

This was a preliminary study evaluating the feasibility of performing arytenoid adduction from an anterior approach using a novel apparatus consisting of Gore-Tex suture threaded through a curled wire with a hook at the end. This was later renamed the “Voice Restoration Device” and will be referred to as such in this conclusion chapter.
Five conditions were evaluated in four excised canine larynges: normal; simulated paralysis; thyroplasty; thyroplasty with arytenoid adduction performed using the traditional posterior approach; and thyroplasty with arytenoid adduction performed using an anterior approach and the Voice Restoration Device. Anterior arytenoid adduction led to significant decreases in threshold aerodynamic and perturbation parameters as well as a significant increase in signal-to-noise ratio. Importantly, parameters for the anterior arytenoid adduction condition were comparable to those for the traditional arytenoid adduction procedure. Further studies evaluating long-term stability in an in vivo animal model are needed.

B.7 Excised larynx evaluation of wedge-shaped adjustable balloon implant for minimally invasive type I thyroplasty

This study addressed two limitations of our initial study on the adjustable balloon implant: an inability to medialize the posterior vocal fold and the need for a traditional thyroplasty window approach with stabilizing frame. A wedge-shaped adjustable implant could be inserted via an anterior minithyrotomy, would remain stable within the vocal fold without the need for a stabilizing frame, and would conform better to the natural shape of the vocal fold and thus medialize the entire vocal fold. Lastly, the use of a wedge rather than a sphere would allow for preservation of the inner perichondrium if desired.

Three conditions were evaluated: normal; simulated unilateral paralysis; and thyroplasty using the wedge-shaped adjustable balloon implant. Threshold aerodynamic and perturbation parameters were significantly decreased with thyroplasty compared to paralysis, and not significantly different compared to normal. The mucosal wave was preserved after implant insertion. Considering the weaknesses of videokymographic analysis in the previous studies due
to differing subglottal pressure input, new parameters aimed at addressing key issues relevant to this study were used. Interfold phase difference, difference between right and left vibratory amplitude, and amplitude of the implanted fold were evaluated. There were no differences among conditions for interfold phase difference or difference between vibratory amplitudes. Amplitude of the fold within which the implant was inserted was significantly greater than zero according to a one-sample t-test.

Effective medialization was accomplished and an improved aerodynamic profile compared to that observed with the spherical implant was achieved. Inserting the implant through only a small minithyrotomy opening was feasible. Preserving the inner perichondrium was not attempted in this study, but is theoretically possible if the opening were more lateral.

B.8 Summarizing table

This table summarizes the gaps in knowledge addressed by each study as well as the salient findings. IL = injection laryngoplasty; ML = medialization laryngoplasty; AA = arytenoid adduction; TVFMI = titanium vocal fold medializing implant.

<table>
<thead>
<tr>
<th>STUDY</th>
<th>GAPS IN KNOWLEDGE</th>
<th>FINDINGS</th>
</tr>
</thead>
</table>
| Multiparameter comparison of IL, ML, and AA | • Does adding AA improve phonatory outcome?  
• How do IL and ML compare?  
• Is one treatment optimal? | • ML-AA produced optimal outcome  
• ML and IL produced comparable outcomes, though mucosal wave amplitude was reduced for IL  
• ML-AA was optimal in this study |
| Multiparameter analysis of TVFMI | • What is the effect of the TVFMI on phonatory aerodynamics?  
• What is the effect of the TVFMI on quantitative acoustic parameters?  
• What is the effect of the TVFMI on the mucosal wave? | • Insertion of the TVFMI significantly decreased threshold aerodynamic parameters  
• Insertion of the TVFMI decreased perturbation parameters and increased signal-to-noise ratio  
• Mucosal wave was preserved |
### Optimal AA based on quantitative real-time voice analysis

- How do phonatory parameters change while the arytenoid is rotated during AA?
- Can vocal efficiency and perturbation parameters be used to guide AA?
- Does optimal arytenoid position determined using vocal efficiency coincide with optimal position for other phonatory parameters?
- Vocal efficiency increased until optimal arytenoid position was reached, and then decreased
- Perturbation parameters decreased until optimal arytenoid position was reached, and then increased
- Vocal efficiency and perturbation parameters were sensitive to arytenoid position and could help guide AA
- Mucosal wave amplitude and threshold aerodynamics also reached local extrema at the same arytenoid position

### Preliminary investigation of adjustable balloon implant

- Can medialization be accomplished with an adjustable balloon implant?
- Does use of an inflatable implant lead to impaired vibration?
- Can a frame be used to hold the implant within the larynx?
- Effective medialization was achieved
- The mucosal wave was not impaired
- The metal frame secured the implant to the thyroid cartilage and helped direct the force of the spherical implant medially

### Classification of glottic insufficiency and tension asymmetry using multilayer perceptron

- Can pattern recognition be applied to identification of glottic insufficiency and tension asymmetry?
- Is classification improved with more parameters?
- What parameters are most useful?
- Samples were classified with 84% accuracy
- Highest classification was observed when using all parameters
- Aerodynamic and acoustic parameters appeared more valuable than videokymographic in this study
- Alternative acoustic and videokymographic parameters should be explored

### Initial investigation of anterior approach to AA in excised larynges

- Can AA be performed from an anterior approach?
- Are results comparable to those obtained from a posterior approach?
- AA was performed successfully from an anterior approach using the Voice Restoration Device
- Results were comparable to those obtained using the traditional posterior approach

### Excised larynx evaluation of wedge-shaped adjustable balloon implant for minimally invasive ML

- Can medialization be accomplished with a wedge-shaped adjustable balloon implant?
- Can effective medialization be achieved through a minithyrotomy approach?
- Does a wedge-shaped implant provide a superior aerodynamic outcome to that observed with the spherical implant?
- Effective medialization was achieved
- The minithyrotomy approach was adequate for inserting the implant and medializing the vocal fold
- Threshold aerodynamics were restored to near normal levels

### C. REVIEW OF WORK IN CONTEXT OF CURRENT LITERATURE

C.1 Adding arytenoid adduction after thyroplasty improves phonatory outcome
The potential benefit of arytenoid adduction after medialized thyroplasty has been the topic of debate, particularly considering the technically challenging nature of the procedure and potential for added morbidity. We found combined thyroplasty-arytenoid adduction to produce the best phonatory outcome compared to injection or thyroplasty alone (Hoffman 2010). This finding is in accordance with several clinical investigations. Kraus reported favorable outcomes following arytenoid adduction, but also had an 18% complication rate in a study of 28 patients (Kraus 1999). In a study retrospectively comparing patients undergoing MT and simultaneous MT-AA, patients undergoing MT-AA had significantly better vocal improvement and patient satisfaction (McCulloch 2000). Adding arytenoid adduction can result in better closure of a posterior glottic gap than thyroplasty alone and can even decrease the likelihood of implant extrusion as the medially placed AA suture promotes implant stability (Abraham 2001). It has also been shown to have a greater impact on normalizing airflow and maximum phonation time (Mortensen 2009).

Other studies have reported that adding arytenoid adduction does not significantly improve outcome. Li et al. found that adding arytenoid adduction did not significantly affect glottic closure or vertical vocal fold asymmetry (Li 2011). Similarly, Chester and Stewart found no clear added benefit to add arytenoid adduction in an evidence-based review (Chester 2003). Importantly, only three studies were included in the review.

Discrepancies in findings across studies could relate to the person performing the procedure, the patients undergoing the procedures, or a combination of both. Surgeon-related factors include choice of implant and experience with both thyroplasty and arytenoid adduction. Patient-related factors include severity (i.e., size of glottic gap) and presence or absence of
concomitant vertical asymmetry. Thyroplasty and arytenoid adduction are different solutions to a similar problem. Thyroplasty achieves medialization by mobilizing the membranous vocal fold with an implant while arytenoid adduction closes the posterior glottis by rotating the arytenoid. The decision to perform one or both largely depends on whether the patient has the two main indications for arytenoid adduction: a large posterior glottal chink or vertical vocal fold asymmetry. A weakness of studies evaluating the added benefit of arytenoid adduction is that different patients undergo thyroplasty alone versus combined thyroplasty-arytenoid adduction. This precludes isolation of arytenoid adduction as the only variable present and is a strength of our study, even though it was conducted in a simplified excised larynx model.

C.2 The titanium vocal fold medializing implant is easy to insert and has a favorable effect on laryngeal function

The titanium vocal fold medializing implant was introduced by Dr. Gerhard Friedrich in 1999 (Friedrich 1999). In his initial set of 20 patients, he observed a reduction in operative time as well as significant improvements in glottic closure and vocal function. Similar results were observed by Bihari et al. (Bihari 2006) and Schneider et al. (Schneider 2003). Importantly, medialization did not adversely affect respiration (Schneider 2003).

Findings from our excised larynx experiment were in accordance with those described above, but performing the experiment in excised larynges allowed us to offer a more rigorous quantitative analysis on a wide range of phonatory parameters (Witt 2010). This study provided additional quantitative support for an implant not commonly used in the United States. Considering the ease of use compared to carving Silastic and the ability to achieve a range of
degrees of medialization with a single implant, it is an attractive and perhaps underutilized device.

C.3 Quantitative voice analysis can guide phonosurgery

One challenge of vocal fold medialization is determining optimal vocal fold position. We addressed this issue in arytenoid adduction by evaluating changes in vocal efficiency and perturbation parameters during arytenoid rotation (Hoffman 2011). This experiment was motivated by our previous study which performed arytenoid adduction without real-time quantitative analysis (Hoffman 2010). If we consider that as a control group, outcomes were better when using the real-time analysis. Two studies have performed real-time voice analysis in humans with some success. Guzman et al. analyzed spectrograms and fundamental frequency while performing Gore-Tex medialization thyroplasty (Guzman 2012). While promising, this study did not include a control group and thus did not determine if intraoperative voice assessment provided an added benefit over subjective evaluation. Matar et al. performed direct measurements of subglottal pressure during medialization thyroplasty to determine which size Montgomery implant to use (Matar 2012). Similar to the Guzman et al. study, analysis seemed beneficial but no control group was included to confirm added benefit. One potential concern of performing detailed voice testing is that it could increase procedural duration, leading to increased swelling which would then render the voice measurements less meaningful. Matar et al. noted that taking direct measurements of subglottal pressure via the cricothyroid membrane did not increase procedural duration or patient discomfort (Matar 2012).

C.4 An adjustable implant can achieve effective vocal fold medialization while offering minimally invasive postoperative modification
As small changes in degree of medialization can have a significant impact on phonation, an adjustable implant is potentially useful. There is one other adjustable laryngeal implant, but that would not be able to be adjusted easily postoperatively without a second operation. Desrosiers et al. proposed an adjustable titanium implant which is inserted via a traditional window, affixed with six screws, and adjusted using two central screws (Desrosiers 1993). The implant was shown to be effective in a cadaveric larynx experiment as well as a clinical trial in 53 patients (Dean 2001). This concept is interesting and could be useful; however, it is “adjustable” in the same sense that the titanium vocal fold medializing implant or Gore-Tex is adjustable. That is, it is adjustable intraoperatively but still requires a second operation should postoperative adjustment be desired. Thus, in the context of the hypothesis that one implant can offer varying degrees of medialization, our study is similar to that from Derosiers et al. However, the key potential benefit of the adjustable balloon implant is that it could be adjusted postoperatively in a minimally invasive fashion without the need for a second operation.

C.5 Pattern recognition can be used to identify voice disorders and classification ability is improved by including a variety of parameters

Pattern recognition using artificial neural networks (ANNs) has numerous applications in medicine. ANNs are powerful mathematical models use nonlinear statistical analysis to classify data into groups (Cross 1995; Baxt 1995). Relevant to this dissertation, pattern recognition techniques have been used to evaluate voice disorders. Wang and Jo classified sustained vowels into three groups: normal; mildly pathological; and severely pathological (Wang 2007). Using Gaussian mixture models, support vector machines, hidden Markov models, and artificial neural networks, data were classified at rates approaching or exceeding 90% (Wang 2007). Similar to
our study (Hoffman 2012), a variety of acoustic parameters were used. However, cepstral analysis was also performed and no aerodynamic or vibratory measurements were included. As cepstral analysis has potential for disordered voice analysis (Heman-Ackah 2003), this may account for the rather high classification rates despite only including acoustic parameters. Sarria-Paja et al. used hidden Markov models to classify data as normal or pathological and achieved classification rates between 80-90% (Sarria-Paja 2010). Pattern recognition has also been applied to differentiate between patients with muscle tension dysphonia and adductor spasmodic dysphonia (Schlotthauer 2010).

Our study adds to the growing body of evidence supporting the use of classification models for clinical decision-making. As computing power increases exponentially, scientific investigation may undergo a transformation from enhancing understanding to improving classification (Krakauer 2013). Moving forward, increasing the number of parameters included in classifications as well as increasing the complexity of which parameters are included may improve classification rates.

C.6 Arytenoid adduction can be performed from an anterior approach

The most challenging aspect of arytenoid adduction is identifying and manipulating the muscular process of the arytenoid from the posterior larynx (Slavit 1992; Mahieu 1989; Slavit 1994). Accordingly, there has been a recent surge in studies attempting to perform arytenoid adduction from an anterior approach, thus eliminating the most challenging aspect of the procedure: accessing the posterior larynx. Considering the variety of methods proposed, apparent efficacy, and mechanical simplicity, it is somewhat surprising that such methods were not introduced sooner. Arytenoid adduction was proposed by Isshiki 1978. Since then, it has
consistently been described as technically challenging but is also known to be effective when performed correctly.

Thus far, five methods have been proposed. Hess proposed the sling arytenoid adduction, where a monofilament thread is slung around the muscular process of the arytenoid via an external approach (Hess 2010). This is a promising new method which was demonstrated to be effective in five excised larynges and two patients; however, there is potential for infection due to the endoluminal routing of the monofilament thread and it is unknown if the sling method can keep the arytenoid fixed over time. Friedrich et al. used suture attached to a screw anchored in the fovea oblonga of the arytenoid (Friedrich 2012). Murata et al. used a method similar to that proposed by Hess, where needles are passed through the thyroid cartilage containing sutures which are then looped around the arytenoid (Murata 2011). Henry Hoffman and colleagues used a novel device consisting of a curled wire attached to a rod which could then be turned one direction to adduct the arytenoid and the other to abduct it (Hoffman 2013). We used suture attached to a hooked wire to accomplish the same goal. Kwon et al. took an alternative approach and manipulated the arytenoid using a cricoid implant inserted from a superior approach (Kwon 2007). One advantage of our method is its ability to accomplish the procedure without needing to pass a device (e.g., screw) through the arytenoid itself. Most of these studies were initially conducted in cadaveric larynges. While only minimal force is required to rotate the arytenoid, long-term stability of all these methods is a key concern.

C.7 Effective medialization with a wedge-shaped adjustable implant can be achieved through a minithyrotomy
This study combined two main objectives. First, we evaluated whether a wedge-shaped implant could provide effective medialization, particularly of the posterior glottis. Second, we evaluated whether the implant could be inserted through a minithyrotomy. The first objective combines principles of an adjustable, inflatable implant (C.4) with implant shape. The wedge shape mimics that provided by Silastic or the titanium vocal fold medializing implant, offering a shape which conforms to the natural shape of the paraglottic space, medializing minimally anteriorly and maximally posteriorly.

Use of a minithyrotomy for implant insertion is well suited for implants whose size can be manipulated. A key example is expanded polytetrafluoroethylene, or Gore-Tex. Insertion through a small opening has been described by McCulloch and Hoffman (McCulloch 1998) as well as Stasney et al. (Stasney 2001). An opening of similar size was created in our size as that described by Stasney et al., approximately circular with a 3-4 mm diameter. They achieved satisfactory outcomes in 25 of 26 patients included in the study. The minithyrotomy approach was also used by Dailey et al. to insert a composite thyroid ala perichondrium flap to augment Reinke’s space (Dailey 2011). The success observed in cadaveric and clinical studies with the minithyrotomy approach demonstrates the potential for minimally invasive vocal fold medialization and voice restoration.

D. CLINICAL CONTEXT

D.1 Current phonosurgery concerns and relationship to proposed interventions

Current mechanical management of glottic insufficiency has several limitations which served as the motivation for this series of studies. Postoperatively modifying the degree of
Medialization is challenging and typically requires a second surgery with corresponding cost, inconvenience, and potential morbidity. An adjustable implant which could be modified in an office-based minimally invasive procedure would decrease patient temporal and financial burden as well as encourage patients and physicians to pursue an optimal, rather than simply acceptable, outcome. This could be particularly useful for patients with progressive disorders such as presbylaryngis, or patients who use their voice professionally for whom restoration of normal or near normal voice quality is critical to livelihood (Woo 2001; Anderson 2003).

Medialization thyroplasty (MT) is simple conceptually but rather challenging in practice. A key factor attracting me to this area of study is the straightforward, mechanical nature of the procedure. As with most topics in medicine, interpretation of something as simple often only indicates a lack of knowledge. Several considerations beyond just achieving medial displacement of a vocal fold are important and relevant to this series of studies.

Some authors place great importance on preserving the inner thyroid perichondrium, but doing so can prevent adequate medialization (Friedrich 1999; Montgomery 1993; Wanamaker 1993). It would be difficult to preserve the perichondrium while performing MT with the sphere-shaped adjustable balloon implant, but preservation would be feasible if using a small wedge. Notably, the perichondrium was violated in the previously described excised larynx studies and a smaller wedge would likely be required if preserving the perichondrium was necessary.

Secondly, the role played by the specific material comprising the implant is not entirely known. Relevant to the adjustable balloon implant, there are potential concerns regarding silicone allergy (Hunsaker 1995) and poor fixation due to silicone not connecting to surrounding tissues (Friedrich 1999; Flint 1997). Additionally, shortcomings and complications of silicone
breast implants are well-documented in the plastic surgery literature, including numerous reports of implant rupture (McLaughlin 2007; Goodman 1998; Brown 1997). Importantly, the tendency for an implant to rupture is dependent on controllable factors such as wall thickness and filler material (Lim 2013; Peters 1998). Texture is a key consideration for breast implants and drove initial changes in implant design towards thinner walls and less viscous gel fillers; this resulted in frequent shell rupture and removal from market in the early 1990s (Lim 2013). While saline implants have a less natural feeling and can thus be undesirable for breast applications, texture is not a critical consideration in MT. Though the evidence relating silicone gel bleeding and connective tissue disease or cancer is weak (McLaughlin 2007), use of saline would also obviate these potential concerns. Wall thickness could also be increased to a level which is more likely to prevent rupture.

Further insights into potential host response can be gained from animal studies evaluating different implants in the larynx. Ustundag et al. observed fibrous capsule formation with minimal allergic or inflammatory response six months after insertion of a silicone implant in the larynx of rabbits, concluding that no adverse foreign body reaction occurred (Ustundag 2005). It is important to note that this experiment used a solid silicone implant, and there could be a concern that any pressure exerted on a fluid-filled implant could cause implant rupture. Gore-Tex and irradiated costal cartilage implants were also evaluated, with incomplete capsule formation and a minimal chronic inflammatory response occurring with Gore-Tex while a severe allergic response and implant resorption occurred with the cartilage implant (Ustundag 2005).

A third key factor is potential for airway compromise (Weinman 2000). Airway compromise is a rare, but potentially life-threatening complication of MT and can be due to
excessive medialization, hematoma formation, edema, or implant extrusion. In the early 1990s, Tucker et al. recommended thyroplasty be done as an inpatient procedure, with patients kept overnight for observation (Tucker 1993). In their series of sixty patients, six experienced a significant complication, with all exhibiting hematoma formation and four also experiencing implant extrusion. Later series have been less conservative, with most advocating the procedure be performed on an outpatient basis (Weinman 2000; Cotter 1995). The risk of implant extrusion generally increases if the perichondrium is violated. The small opening created for the minithyrotomy approach described in chapter 8 would be too small to allow for lateral extrusion. Medial extrusion, which raises concerns of airway compromise, would be more likely. Aforementioned findings from the Ustundag et al. study increase the confidence that the implant could be secured by the fibrous capsule, but the host reaction in persons with a silicone allergy may increase the likelihood of extrusion.

A fourth issue surrounding MT which has been the subject of significant research is the use of an implant to correct a posterior glottic gap. Regardless of how well an implant is shaped, it is not ideally suited to close the posterior glottis. The arytenoid must be manipulated as well, though procedures capable of doing this such as arytenoid adduction (Isshiki 1978) or arytenopexy (Zeitels 1998) are technically challenging and thus often avoided (Damrose 2003). The recent surge in interest to perform arytenoid adduction from an anterior approach (Hess 2011; Friedrich 2012; Murata 2011; McCulloch 2013) combined with studies reporting improved outcomes with simultaneous MT-AA compared to AA alone (McCulloch 2000; Abraham 2001; Mortensen 2009) provide evidence that the procedure has a place in the management of vocal fold paralysis but current techniques are inadequate. Anterior arytenoid adduction significantly
decreases the difficulty of performing the procedure by eliminating its most challenging aspect: accessing the posterior larynx. The availability of an easier procedure that has been shown in our preliminary excised larynx study to produce comparable results (McCulloch 2013) may increase the frequency with which arytenoid adduction is performed and thus improve the clinical outcomes of patients with glottic insufficiency.

D.2 Value of minimally invasive procedures

There is a general trend in medicine towards less invasive procedures. An excellent new example is transaxillary thyroidectomy (Landry 2010). Neck scars are easily visible and can become a serious concern for patients (Durani 2009). For the patient with a serious voice disorder, a scar may seem a reasonable price to pay to regain vocal function, until vocal function is achieved and the patient’s primary problem is now the scar. Exploring modifications to procedures such as implant insertion method or even point of entry is warranted to improve patient satisfaction. Decreasing invasiveness has the additional potential benefits of facilitating a transition from the operating room to the office, decreasing procedural time, eliminating the need for anything but local anesthesia, and decreasing health care delivery costs.

While a central goal of this line of research is to make permanent vocal fold medialization less invasive, it is important to proceed cautiously in a controlled environment with initial trials performed on an inpatient basis to allow for close observation. Specifically, it may be challenging to maintain meticulous hemostasis during anterior arytenoid adduction, as visibility is significantly less than that with an open procedure. Importantly, though, it is not necessary to access the posterolateral larynx when performing this method; this aspect of the
traditional procedure is a major cause for postoperative bleeding and hematoma formation (Weinman 2000).

D.3 Use of quantitative voice parameters to promote evidence-based medicine

There is a relatively recent push in medicine towards objective, evidence-based management (Merati 2006; Sackett 1995). Key to promotion of evidence-based medicine is development of reliable outcome measures capable of evaluating and comparing interventions. There are numerous aspects of laryngeal function which can be quantified, though doing so objectively can be challenging. Measurement reliability, utility, and ease are critical factors dictating whether a new test or parameter will gain widespread acceptance. The parameters used in this study are valuable individually, but more valuable collectively. As voice production is a complex process, dysphonia is multidimensional and single parameters may be ill-suited to characterize it completely (Aboras 2010; Yu 2001). Evaluating voice input and output as well as the vibration occurring at the interface can help provide a more complete picture of laryngeal function.

Critical to useful implementation of objective voice assessment is knowledge regarding measurement reliability. Leong et al. evaluated measurement reliability of a variety of commonly used acoustic parameters in normal subjects and found that reliability varied dramatically across parameters (Leong 2013). Reliability also appeared different between male and female subjects, though only eighteen total subjects (nine males and nine females) were included in the study. Importantly, performing a multiparameter assessment and obtaining a more complete picture of laryngeal function may mitigate the limitations associated with single measurement variability.

D.4 Concerns regarding inflatable implant
While a preliminary excised larynx experiment evaluating a new thyroplasty implant can provide important information on biomechanics, important factors such as host response and long-term stability cannot be measured. A fibrous capsule is known to form around solid silastic implants in the larynx and fluid-filled silicone implants in the breast. In some cases, the capsule formed around a breast implant can be so hearty as to prevent leakage of fluid once the integrity of the implant wall has been compromised (Goodman 1998). This has implications for the adjustable balloon implant and raises questions regarding its potential clinical utility. Importantly, how soon does the fibrous capsule form? Along the same lines, over what time span can the volume of the implant be modified? Can capsule formation be delayed by application of biochemical agents to the exterior of the implant? Hester and colleagues have had significant success applying both a polyurethane coating as well as an acellular dermal matrix to decrease capsule formation and prevent capsular contracture (Hester 1988; Hester 2012). Minor complications such as rash or Mondor’s disease (thrombophlebitis of the superficial veins of the breast) may occur, but are benign and self-limited (Gasperoni 1992). Follow-up after insertion of dermal matrix-covered implants has been up to 3.5 years, with minimal incidence of contracture (Hester 2012). Local immunomodulation is a second possible means of preventing adverse host response. Dolores et al. examined the cellular and molecular composition of fibrous capsules surrounding silicone breast implants and found them to contain massive amounts of fibronectin and tenascin as well as accumulation of macrophages, fibroblasts, and CD4+ T-cells (Dolores 2004). Reducing or preventing the local immune reaction may improve implant biocompatibility and life span (Dolores 2004). Future in vivo animal studies on the adjustable balloon implant
would be improved by including a treatment group using implants coated with polyurethane, acellular dermis, or immunomodulating agents.

A central concern regarding capsule formation and contracture is implant rupture and potential consequences. It would be desirable to prevent rupture by modulating host response, but it is important to consider how rupture would affect laryngeal function. Importantly, filling the implant with saline rather than silicone gel eliminates concerns regarding leakage of implant material into surrounding tissue and possible, though heretofore unproven (McLaughlin 2007), pathologic sequelae (Brown 2001). Saline-filled implants have been found to be safe with 96.9-98.9% implant survival at 10 years (Cunningham 2000). The second concern would be loss of medialization. This situation may be analogous to that following extrusion of a solid implant, in that the medializing force provided by the implant is now absent and only host factors determine vocal fold position. Surprisingly, there are reports of preserved vocal fold medialization even after implant extrusion (Al-Yousuf 2006); however, voice quality often deteriorates following extrusion (Halum 2005). If the implant were simply leaking from the access port, the implant could be re-filled and the port re-sealed. Cunningham et al. conducted a multicenter review and found a saline-filled breast implant deflation rate of approximately only 1% per year, unaffected by original volume (Cunningham 2000). If implant integrity was compromised, a revision procedure would have to be performed. One potential advantage of using an inflatable implant is that this revision may possibly be accomplished as a minor procedure, though the feasibility of this would depend on host response and potential adhesion to the implant, which would prevent smooth removal and necessitate an open procedure.
E. SCIENTIFIC CONTEXT

E.1 Value of ex vivo model

The excised larynx model provides an opportunity to evaluate the physiology of phonation directly from multiple perspectives. Input, output, and vibration can be quantified with ease. Historically, excised larynx experiments have led to significant contributions to our knowledge on laryngeal physiology. The first excised larynx experiment is thought to have been conducted by Leonardo da Vinci, who demonstrated that a cadaveric larynx could still produce sound provided air was passed through it (da Vinci 1952). The variables which affect phonation can be systematically monitored and independently controlled, which cannot be achieved in an in vivo animal model or human subject.

Excised larynx experiments have three key advantages relevant to this series of studies. First, one can evaluate new procedures and devices without any risk to an animal or patient or need for regulatory approval. This allows for development of preliminary evidence to support further animal or human subject testing once the device is optimized. Second, the effect of treatment on phonation can be immediately and easily quantified. While animal studies would require delayed periods between creation of the injury and device insertion and then between device insertion and treatment evaluation, all steps can be performed within one day during an excised larynx experiment. Lastly, a wide range of parameters can be measured. If performing a study using human subjects, each additional test required to measure a parameter increases the burden placed on the patient. Most voice tasks are rather painless, but some such as high-speed videoendoscopy can be uncomfortable, particularly for those with a sensitive gag reflex.
Measurements obtained from excised larynges are also objective and not subject to variability associated with subject performance.

While excised larynx experiments are useful, they have well-documented limitations. Relevant to this proposal, they cannot study the influence of neuromuscular contraction (Berke 2007) or variations in neural input such as may occur with paralysis versus paresis versus glottic insufficiency of a non-neural etiology (e.g., vocal fold scar). True vocal fold paralysis results in more than simply an inability to medialize the vocal fold; muscular atrophy is also present which was not included in the excised model used in this series of studies. Most notably, excised larynx experiments cannot provide information on long-term stability or host response, both of which are key considerations in biomedical implant development.

E.2 Real-time monitoring of functional voice parameters

Of the studies included in this dissertation, the use of intraoperative real-time monitoring of quantitative, objective voice parameters (Hoffman 2011) may be most readily applicable. We employed measurements of both vocal efficiency (acoustic power divided by aerodynamic power) as well as perturbation parameters (percent jitter and percent shimmer) in determining the optimal degree of arytenoid rotation when performing arytenoid adduction. The appropriate degree of arytenoid rotation is currently determined using subjective assessments of intraoperative patient phonation, but it can be challenging for the clinician to remember which orientation produced optimal voice production.

Guzman et al. (2012) and Matar et al. (2012) recently used real-time measurements of acoustic and subglottic pressure signals, respectively, to guide thyroplasty. Preliminary results were encouraging and led to good voice outcomes, though no control group was included in
either study. While intraoperative voice assessment is promising, it is important to remember that the most important function of the larynx is maintaining the airway. It is possible that a phonatory parameter may be optimized when the vocal fold is in a slightly hyperadducted position, which may cause slight respiratory compromise such as dyspnea on exertion. Before intraoperative voice assessment can be applied routinely and reliably, it would be beneficial to know if optimal vocal fold position for phonation corresponds to optimal position for respiration. Preoperative assessment and finite element modeling coupled with intraoperative assessment may facilitate determination of optimal vocal fold position.

E.3 Effects of medialization on vocal fold contour and resultant effect on phonation

Vocal fold contour has significant effects on voice quality and efficiency. When performing medialization, one must consider not only the transverse plane but also the coronal plane (Mau 2012). Vocal efficiency increases and phonation threshold pressure decreases as the glottis becomes more rectangular (Titze 1979; Chan 1997; Mau 2012). However, excessive medialization can adversely affect phonatory quality by serving as a nidus for airflow turbulence (Grisel 2010). Preoperatively determining the optimal glottal configuration could guide phonosurgical intervention. Mittal et al. have been conducting pioneering work in the area of modeling-based planning for medialization thyroplasty (Mittal 2011). Coupling preoperative assessment with finite element models of vocal fold vibration may facilitate development of hypothesis-driven implant shapes designed to create the optimal vocal fold contour for a specific patient.

F. LIMITATIONS
F.1 Ex vivo model

As noted above, excised larynx experiments have key limitations relevant to this series of studies. Most notable are the lack of a host response and inability to evaluate long-term stability. While meaningful predictions can be gleaned from the silicone breast implant literature and previous in vivo animal experiments using solid silastic thyroplasty implants, it is important to conduct carefully designed animal experiments to evaluate the new devices. This would also allow for evaluation of swallowing and respiratory outcomes following intraoperative quantitative feedback-assisted thyroplasty and arytenoid adduction.

F.2 Acoustic analysis

Voice signals can be classified according to type, where type 1 signals are periodic, type 2 signals contain subharmonics, and type 3 signals are chaotic (Titze 1995). Perturbation analysis is ideally suited for type 1 signals, while nonlinear dynamic analysis is preferred for type 2 or 3 signals. However, high-dimensional chaotic voice characterized by the presence of stochastic noise, such as that found in the breathy phonation resulting from glottic insufficiency, is not addressed in this current scheme (Sprecher 2010). Current nonlinear dynamic parameters such as correlation dimension seek to quantify the amount of variables needed to describe a complex system. While this parameter is capable of quantifying sound produced by actual vocal fold vibration, it is incapable of quantifying signals which contain a prominent breathy, or noise, component (Sprecher 2010; Awan 2010). Perturbation analysis was used in this series of studies as nonlinear analysis is incapable of evaluating breathy phonation, such as that produced by the excised larynges with simulated vocal fold paralysis. It would be preferable to use more complex methods of analysis capable of quantifying high-dimensional chaos, but none are currently
available. As glottic insufficiency is the primary anatomic etiology of dysphonia (Isshiki 1998), developing such parameters is warranted for both clinical assessment and scientific inquiry.

**F.3 Vibratory analysis**

High-speed videokymography is a useful tool which can quantify key characteristics of the mucosal wave such as amplitude or phase difference. However, mucosal wave amplitude is affected by subglottal pressure input. A key tradeoff when conducting this research was sacrificing direct comparisons (i.e., evaluation of acoustic parameters across conditions at the same aerodynamic input) to enable quantitative comparisons. As the phonation threshold pressure for the paralysis condition often exceeded the phonation instability pressure for normal or treatment trials, it was not possible to obtain measurements for voice parameters at the same subglottal pressure input across trials.

Even with different aerodynamic input, videokymography can provide information on vibrational symmetry between the two folds. This is useful to confirm that the implant is not placing excessive pressure on the lamina propria and impeding oscillation. This can be accomplished by quantifying intrafold phase difference, as the movement of the inferior vocal fold lip occurs before that of the upper vocal fold lip. Amplitude of the fold into which the implant was inserted can also be evaluated to confirm that intervention did not adversely affect vibratory mechanics and impinge on the mucosal wave. This situation could arise if an inflatable implant were filled excessively, thus placing pressure on the lamina propria and preventing normal vibration.

In the future, other methods of quantifying vocal fold vibration will be explored. Phonovibrography describes movement of the vocal fold along its entire length, rather than a
single pixel line as in videokymography, and has shown promise in evaluating vocal fold paralysis (Lohscheller 2008).

G. AREAS FOR FUTURE STUDY

G.1 In vivo evaluation of adjustable balloon implant and anterior arytenoid adduction

The most important step in further developing the adjustable balloon implant (Hoffman 2011) and Voice Restoration Device (McCulloch 2013) is conducting in vivo canine studies. This will allow us to evaluate host response as well as long-term stability and, in the case of the balloon implant, adjustability. Conducting live animal studies will allow us to transect the recurrent laryngeal nerve, thus creating a true model of vocal fold paralysis.

Important questions to be answered by the animal studies regarding the adjustable balloon implant include: does a fibrous capsule form around the implant? If so, does it preclude late modifications to implant volume? If capsule formation is detrimental to implant efficacy, can it be prevented by applying polyurethane or acellular dermal matrix, as has been done with silicone breast implants (Hester 1988; Hester 2012)? Can the implant volume be adjusted easily? The motivation in proposing the implant was to provide something which could offer minimally invasive postoperative medialization adjustment; it is important to verify that this theoretical benefit can be realized in practice. Cunningham et al. found that saline-filled silicone breast implants leak at a rate of approximately 1% per year (Cunningham 2000). Is the rate comparable for the adjustable balloon implant? Determining the precise rate may require long-term animal studies, but insights into whether the implant leaks could be gained by evaluating volume after duration as short as six months. While the primary objectives of in vivo animal studies would be
to evaluate ease of implantation, host response, and long-term stability, living animal experiments would also offer the opportunity to determine how respiration and deglutition are affected. Nomura et al. evaluated respiratory and swallowing outcomes in canines following implantation of a neuromuscular stimulator to treat bilateral vocal fold paralysis (Nomura 2010). A clever method of evaluating glottic closure during swallowing was employed: an inferior view of the glottis was obtained via transtracheal endoscopy to confirm posterior cricoarytenoid stimulation during respiration did not result in glottic incompetence during swallowing. A similar approach could be implemented to confirm that normal glottic closure has been restored following unilateral medialization. Similarly, treadmill exercise experiments could be performed to gauge respiration and exercise tolerance as were done by Nomura et al. This would allow us to confirm that the vocal fold had not been medialized excessively.

Similar questions are relevant for in vivo animal experiments evaluating the Voice Restoration Device. Specifically, does the device remain stable within the larynx over time and what is the host response to it? It is possible that the arytenoid may become fixed in the position dictated by the device and long-term stability (i.e., stability over the patient’s lifetime) is not actually necessary. Evaluating arytenoid stability over the first year may help answer this question. Further considerations unique to this device are discussed in section A.4.

G.2 Intraoperative quantitative voice monitoring

Our excised larynx study using real-time measurements of perturbation parameters and vocal efficiency demonstrated these parameters were sensitive to arytenoid position (Hoffman 2011). Percent jitter and shimmer reached a local minimum while vocal efficiency reached a local maximum nearly simultaneously and the arytenoid position corresponding to that point was
considered to be optimal. Preliminary clinical studies using intraoperative measurement of subglottal pressure or spectrogram analysis have also had promising results (Matar 2012; Guzman 2012). Assessing the benefit of quantitative intraoperative voice assessment is likely the study which is closest to being performed clinically. During thyroplasty and arytenoid adduction, the patient is awake and produces voice when cued to do so by the surgeon. Perturbation parameters could be measured rather easily using only a microphone and the real-time measurement software we designed and used in our excised larynx study. As voice becomes fairly periodic when the arytenoid is placed in a position conducive to phonation, the application of perturbation parameters is valid. The most important measurement, though, is likely vocal efficiency. This parameter describes how well the larynx functions as an energy transducer, considering both aerodynamic input as well as acoustic input (Jiang 2000). Acoustic power could be measured easily using a microphone. Measurement of aerodynamic power (subglottal pressure multiplied by airflow) is more challenging, but still feasible. Subglottal pressure could be measured directly by passing a small tube through the cricothyroid membrane while airflow could be measured using a mask placed over the mouth and nose. While these additions are feasible, it may be challenging to do this in the operating room. As the local extrema for perturbation parameters were reached at the same time as that for vocal efficiency, acoustic assessment alone may be adequate and would certainly be easier to perform.

When evaluating the addition of intraoperative quantitative voice assessment, it would be beneficial to include a control group. This was absent from prior studies evaluating intraoperative voice monitoring and is important if true superiority, rather than simply positive
outcome (which could be obtained even without the aid of voice assessment in the hands of an experienced surgeon), is to be demonstrated.

G.3 Use of Voice Restoration Device to facilitate pharmacologic or radiotherapeutic interventions

While use of the Voice Restoration Device (McCulloch 2013) to perform arytenoid adduction from an anterior approach could be quite useful, its potential in other applications is perhaps more exciting. Once inside the larynx, the Voice Restoration Device creates a therapeutic corridor spanning the length of the vocal fold. This corridor can be used to make mechanical manipulations as in arytenoid adduction or thyroplasty, but it can also be used to perform pharmacological interventions, similar to the drug-eluting stents used in vascular surgery (figure 1). Time-delayed release of steroids could be used in the management of chronic laryngeal inflammation, such as that found in some autoimmune diseases (e.g., Sjogren’s syndrome, rheumatoid arthritis). Controlled release of growth factors could provide a new treatment for vocal fold atrophy. Lastly, anti-neoplastic drug delivery or brachytherapy for stage I or II laryngeal carcinoma would both be facilitated by using the Voice Restoration Device. Chemotherapy and radiotherapy have both demonstrated the ability to cure early laryngeal cancer (Holsinger 2009; Khan 2012; Laccourreye 2001), but are associated with systemic side effects of damage to surrounding healthy tissue. By localizing drug or radiation delivery,
harmful toxicity could be decreased significantly while not compromising treatment efficacy. Each of these approaches would represent a significant shift and improvement in the way these common disorders are treated.

H. UNANSWERED QUESTIONS IN OTOLARYNGOLOGY

There are many opportunities for important research to be conducted within and outside the topic of vocal fold medialization. In addition to the areas for future research described above, additional clinical and basic science questions within otolaryngology are described below, many of which have been prompted by discussions with dissertation committee members.

H.1 What are the possible methods by which a normal voice can be produced?

It is obviously possible to produce a normal sounding voice with two healthy vocal folds; however, it has also been demonstrated that normal voice production can be achieved with one normal vocal fold vibrating against a plexiglass plate (Jiang 1993). Thus, it is conceivable that normal voice could be achieved in any patient with one functional vocal fold. Phonation can thus be thought of as an ellipse, with normal voice occurring on the major axis; both two functional vocal folds as well as one functional vocal fold vibrating against a rigid surface produce a

![Diagram](image-url)

Figure 2. Diagrammatic representation of normal and disordered voice production.
“normal” voice, represented by the major axis vertices (figure 2). Increasing either the space between the vocal folds (moving towards the lower minor axis vertex) or the phase difference between them (moving towards the upper minor axis vertex) results in an increasingly abnormal voice. The fact that normal voice can be achieved with only one healthy vocal fold has implications for medialization procedures as well as oncologic resection. If a unilateral cordectomy or hemilaryngectomy were performed for local control of laryngeal carcinoma, it may be possible to restore normal voice and glottic closure with placement of a rigid implant at the level of the glottis. Similarly, stiffening of one vocal fold either with an injectable or implant would not necessarily degrade voice quality, provided the fold is at the midline, the contralateral fold is functional, and sufficient subglottal pressure can be achieved. It is possible that current medialization procedures do not improve voice by improving the health of the manipulated fold, but rather simply provide a surface against which the contralateral normal fold can vibrate. Basic science studies using the hemilaryngeal setup described by Jiang and Titze (Jiang 1993) could help address these questions.

H.2 How can normal vibration be restored after vocal fold scar?

Vocal fold scarring is considered the most common reason for poor voice quality following phonosurgery (Woo 1994; Berry 2005). Vocal fold scar can deform the vocal fold edge, disrupt the lamina propria, increase vocal fold stiffness, and cause glottic insufficiency (Hansen 2006). Though current treatment of scar is challenging and suboptimal, several promising methods may transform the way this common abnormality is managed.

Potential biochemical candidates include hepatocyte growth factor (Hirano 2004) and mitomycin-C (Garrett 2001). The goal of many of these interventions is to decrease collagen
deposition. Additional prophylactic measures such as vitamin A application (Tateya 2008) or corticosteroids (Camagnolo 2010) also hold promise.

In addition to biochemical interventions, newly proposed surgical interventions may also be beneficial. Dailey et al. recently proposed local vascularized flaps to augment Reinke’s space (Dailey 2011). A vascularized composite thyroid ala perichondrium inserted into the vocal fold demonstrated favorable rheologic characteristics in canines and may be useful in restoring the lamina propria of patients with vocal fold scar. Endoscopic interventions may also be useful. Hoffman et al. performed microendoscopy of Reinke’s space using sialoendoscopes (Hoffman 2008). Direct visualization and exposure of Reinke’s space may allow for targeted delivery of therapeutic agents or lysis of adhesions. The optimal therapy may eventually be a combination of surgical and biochemical methods.

**H.3 Is deep brain stimulation useful for the treatment of spasmodic dysphonia?**

Spasmodic dysphonia (SD) is an incurable, idiopathic focal dystonia affecting the intrinsic laryngeal musculature. Patients with SD experience problems such as social isolation, depression, and decreased quality of life (Baylor 2005). Adductor SD is characterized by a strained or strangled voice quality due to hyperactivity of the thyroarytenoid or lateral cricoarytenoid muscles. Abductor SD is characterized by a breathy voice with hyperactivity of the posterior cricoarytenoid muscles. Current treatment of SD is typically with repeated botulinum toxin injections. Beneficial effects on voice quality last 3-12 months; however, many patients become resistant and require increased injection dosage or frequency (Jankovic 1991). It can also take several injections prior to determining the optimal dose (Holden 2007). Treatment
is associated with side effects such as dysphagia or breathiness due to diffusion away from the active site (Sedory Holzer 1996).

As SD is a focal dystonia, it is likely similar to other focal dystonias with a pathophysiology based in the central nervous system (Ludlow 2008). Treatment for dystonia is typically targeted at increasing inhibition or reducing excitability (Boroojerdi 2003). Deep brain stimulation (DBS) of the internal globus pallidus has been used to treat dystonia (Coubes 2004). It may be a promising treatment for SD not responsive to current treatment approaches, though the reported reduced efficacy of DBS on voice and speech tempers enthusiasm (Deuschl 2006; Ludlow 2008). Further studies on the role of the central nervous system in SD may shed light on which regions could benefit from stimulation.

**H.4 What roles do detailed preoperative imaging and modeling play in phonosurgery?**

Current thyroplasty, particularly with carved Silastic implants, is guided by and thus heavily dependent on experience and intuition (Jin 2006). Window placement and implant size errors are not uncommon and can lead to procedural failure and the need for a revision procedure. Preoperative computer modeling and intraoperative image guidance may help improve outcome consistency when performing thyroplasty. Bielamowicz, Jin, Mittal, and colleagues are conducting excellent work in this area, though studies thus far have been primarily theoretical and methods have not yet been implemented clinically (Jin 2009; Jin 2006; Mittal 2011). Successful application will combine detailed preoperative imaging with sophisticated computer modeling to predict the effects of an intervention.

Incomplete parameterization has limited the clinical application of many vocal fold models (Mittal, 2011). High field micro-MRI can provide imaging detail on the micron scale
Regatte 2007) and could provide the detailed inputs necessary to improve current models. Imaging technologies such as diffusion tensor imaging (DTI) and T2 mapping allow simultaneous characterization of biomechanical properties such as the porosity and water density in the vocal fold substructure and laryngeal musculature. Together, micro-MRI with DTI and T2 mapping can generate highly precise data on laryngeal structure and function, thus connecting anatomy and physiology. Chen et al. recently applied micro-MRI to define the laryngeal cartilage boundaries and quantify cartilage volume and surface area (Chen 2011). To take full advantage of the level of detail offered by micro-MRI, sophisticated modeling techniques are required.

Previous models have over-simplified the complex structure of the larynx. Finite element analysis is a numerical method used to solve equations of continuum mechanics (Tao 2006). These models provide superior approximations of true physiology and can deal with complex boundaries and structures (Tao 2007). Each model is comprised of thousands of individual elements which can be defined by the user. Precise characterization of vocal fold structure afforded by micro-MRI may allow for detailed descriptions of each element. Each element can also be altered to simulate the effects of a disorder, such as by decreasing the number of elements representing the thyroarytenoid muscle to reflect paralysis-induced atrophy. With the development of patient specific finite element models, physicians can predict the effect of phonosurgical interventions on biomechanical parameters and vocal fold vibration, which will help the clinician determine optimal treatment methods, such as how a thyroplasty implant should be shaped or placed, or if an arytenoid adduction is necessary to achieve glottic closure. Complication rates for vocal fold medialization can be as high as 15%, with revision rates as high as 6% (Young 2010; Rosen 1998). Better surgical planning would improve patient outcomes and lower financial and social costs associated
with revisions and complications.

**H.5 How can we treat subglottic stenosis while preserving voice production?**

Subglottic stenosis is a narrowing of the subglottic airway, often caused by prolonged intubation but also occurring congenitally. Patients may present with dyspnea or stridor. Surgical management includes endoscopic, augmentation, and resection procedures (Kelchner 2008). The Myer-Cotton scale grades severity according to degree of airway obstruction (Myer 1994). Grade I or II stenosis may be amenable to endoscopic procedures, while Grade III and IV stenosis requires resection and airway reconstruction, with potential for adverse effects on vocal function (Kelchner 2008; Smith 1993). Resection poses numerous possibilities for damage to structures critical for phonation, including the recurrent laryngeal nerve, anterior commissure, vocal folds, and arytenoids (Baker 2006). Cricotracheal resection, a commonly used open approach, has a high success rate for achieving decannulation but also results in chronic dysphonia (Smith 2008). This procedure requires removal of the cricothyroid muscles which limits pitch range. The use of stents postoperatively to maintain a patent airway can be a nidus for granuloma formation or inhibit normal vocal fold movement (Kelchner 2008). Dysphonia following intervention can be characterized by harshness, false vocal fold phonation, inspiratory phonation, or pitch abnormalities (Bailey 1995). Importantly, etiology and severity of stenosis as well as type, timing, and number of operations all affect voice outcome (Kelchner 2008).

Management of chronic dysphonia following laryngotracheal reconstruction remains one of the greatest challenges in pediatric laryngology (Dohar 2013). Factors which may lead to dysphonia include disruption of the cricothyroid muscles, edema, scarring, changes in the shape of the subglottis, and fixation of the laryngeal cartilages (Houlton 2012). Violation of the conus
elasticus can cause an increase in airflow turbulence which could then lead to aperiodic vocal fold vibration (Khosla 2007; Houlton 2012). Accordingly, key issues to consider when developing modified approaches to the treatment of subglottic stenosis include the importance of subglottic contour, the significance of pitch alteration, and preservation of healthy laryngeal structures. Incorporation of robotic surgery may aid in preservation of healthy structures and facilitate use of an endoscopic rather than open approach, allowing for incision or excision of stenotic segments without compromising critical structures such as the vocal folds. Transoral robotic surgery (TORS) has transformed the management of oropharyngeal malignancies, allowing for minimally invasive surgical access and eliminating the need for open procedures (Villanueva 2013). Behavioral voice therapy training patients how to contract the thyrohyoid muscle forcefully could potentially aid in restoring pitch range lost due to disrupted cricothyroid muscle action. Lastly, computer model-driven shaping of the glottic and subglottic contour could prevent generation of the turbulence which leads to aperiodic phonation. This could conceivably be accomplished using a seeded scaffold with shape designed to mimic the natural subglottic airway. Dr. Martin Birchall’s group has done pioneering work on tracheal replacement, where donor tissue is decellularized and coated with recipient epithelial cells and mesenchymal stem cell-derived chondrocytes (Macchiarini 2008; Elliott 2012). As cell harvesting and processing methods become more popularized and thus less expensive, they may be employed for improving life (i.e., restoring normal voice) as well as prolonging it.

H.6 What role does edema play in nodule formation and how can it be managed?

The vocal fold is a biphasic structure containing both solid and liquid material. During vibration, fluid may accumulate in the middle of the vocal fold, with the degree of accumulation
directly related to vibratory amplitude and frequency (Jiang 1991; Tao 2010). This movement of fluid causes intravascular pressure to increase significantly, potentially predisposing to capillary damage and edema when phonation occurs at high frequencies (Czerwonka 2008). This may play a key role in the pathogenesis of vocal fold nodules and vocal fold edema (Czerwonka 2008). If these benign vocal fold disorders are truly caused by vascular abnormalities, they may be amenable to treatments targeted at blood vessels. Specifically, photoangiolytic laser ablation with the potassium titanyl phosphate (KTP) laser or pulsed dye laser (PDL) may remove damaged vessels while inciting angiogenesis and subsequent resorption of excessive fluid. Alternatively, beta-adrenergic agonists or calcium channel blockers which have been shown to decrease vessel permeability (Parker 1997; Mayhan 1984) may offer pharmacologic agents for prophylaxis or management of benign vocal fold lesions (Czerwonka 2008), which could be particularly valuable if given in a topical preparation at times when vocal abuse is known to be a risk (e.g., vocal performances). Further basic science studies are necessary to confirm the theory. Clinical trials determining whether photoangiolytic laser treatment of vocal fold nodules is effective are also warranted.

**H.7 What is the pathophysiology of benign paroxysmal positional vertigo?**

Benign paroxysmal positional vertigo (BPPV) is characterized by episodic vertigo provoked by changes in head position relative to gravity (Epley 1996). Schuknecht proposed that BPPV is caused by cupulolithiasis, or dense particles in the posterior semicircular canal (Schuknecht 1973). Anatomic studies looking for these substances have had varied results. Parnes and McClure found free-floating particles within the posterior canal when performing canal occlusion for BPPV (Parnes 1992). Kveton and Kashgarian performed electron microscopy
of the labyrinth in ten patients undergoing acoustic tumor removal and found particles in nine, though only one patient had positional vertigo preoperatively (Kveton 1994). Welling et al. evaluated 73 patients without BPPV and 26 patients with BPPV undergoing surgery; no particles were observed in the patients without BPPV while particles were observed in 8 patients with BPPV (Welling 1997). They also evaluated 31 archived temporal bones from patients without a history of BPPV and did not find any evidence of cupulolithiasis. From these studies, it appears otoliths are neither necessary nor sufficient for BPPV. Thus, there may be additional or alternative mechanisms at play.

Epley is a staunch advocate of the cupulolithiasis theory and proposed the canalith repositioning procedure (CRP) to move the otoconia through the canal and back to the utricle, where they no longer affect canal dynamics (Epley 1992). Previously, an alternative theory stated that BPPV is due to a density differential between the endolymph and the cupula of the posterior semicircular canal which can be affected by gravity and cause relative motion (Hall 1979). Interestingly, though physical evidence of the canalith theory is lacking, the CRP is generally found to be successful. Froehling et al. conducted a randomized controlled trial in 50 patients with BPPV to compare the CRP with a sham maneuver (Froehling 2000). Over ten days, symptoms resolved in 50% of the CRP group and 19% of the sham group. A Cochrane Collaboration review conducted by Hilton and Pinder found that the Epley maneuver was more effective than no treatment, but evidence that it provides a long-term “cure” is lacking (Hilton 2012). Amor-Dorado et al. conducted a randomized trial comparing the CRP with the Brandt-Daroff maneuver and found 92.7% of patients treated with the CRP had a negative Dix-Hallpike maneuver at one month (Amor-Dorado 2012). As BPPV is by definition an episodic disorder, it
can be difficult to determine which cases resolved due to the maneuver, which resolved due to fatigue, and which resolved due to time.

While results of these studies support the use of the CRP, they do not necessarily validate the hypothesis that BPPV is caused by otoconia. Interestingly, many articles on the topic begin with a statement such as “Most clinicians agree that…” or “It is generally accepted that…”, a clear indication that the pathophysiology has yet to be clearly elucidated. Considering the reported success rates of the CRP, one may question whether it is even necessary to understand the problem if it can already be treated. However, improving our understanding may yield insights into new treatments, either behavioral or pharmacologic, that can provide not only temporary relief but also long-term relief from this bothersome and sometimes debilitating disorder.

**H.8 What are the long-term effects of surgical intervention on the Eustachian tube?**

The Eustachian tube (ET) plays a critical role in protection, clearance, and ventilation of the middle ear (Van der Avoort 2005). Opening of the ET equilibrates middle ear pressure with atmospheric pressure. ET dysfunction, or an inability to open the ET, is a common condition and a key factor in the pathogenesis of middle ear disease. The impact on patients can be substantial, with common symptoms including otalgia, tinnitus, and aural fullness (Bluestone 2005; Seibert 2006). Quality of life may be adversely affected due to situational avoidance, communicative deficits, and reduced productivity (McCoul 2012). Sequelae of long-term dysfunction include cholesteatoma, chronic otitis media, hearing loss with language delay in children, chronic tympanic membrane perforations, and tympanic cavity atelectasis (Linstrom 2000). Thus, ET dysfunction is a significant problem warranting intervention.
ET dysfunction has traditionally been treated via indirect approaches, such as myringotomy and tube placement. This procedure does not address the underlying ET dysfunction (van Heerbeek 2002) and is associated with complications including purulent otorrhea, myringosclerosis, segmental atrophy, retraction pockets, and perforation of the eardrum (D’Alatri 2012; Vlastarakos 2007). Transnasal endoscopic interventions directly addressing ET dysfunction have been introduced recently. These procedures have shown promising preliminary results (Poe 2003; Poe 2007; Metson 2007), but long-term outcomes are unknown. Further evaluation and development of these procedures is dependent on improving our knowledge of ET physiology and ability to evaluate it.

The ET has traditionally been viewed as a structure which should not be addressed therapeutically, as any attempt to correct dysfunction would only make it permanent. Accordingly, it has been largely ignored and there are no standardized objective measurements of ET function (Handzel 2012). Two available assessments are endoscopy and sonotubometry. Endoscopy only allows for visualization of the nasopharyngeal orifice and does not provide any direct information on function (Lukens 2012). Sonotubometry consists of using a microphone in the external auditory canal to detect sound emitted from the nasal cavity, but false positives and negatives are common (Sumi 2007). Importantly, many subjects report adequate ET opening despite a minimal change in sound pressure level measured in the auditory canal (Di Martino 2010). This phenomenon would likely not occur if the ET opened completely along its length; however, passage of a discrete air bolus could lead to a small or absent increase in auditory canal sound pressure even though ventilation occurred. We used cine computed tomography (CT) to observe the mechanism of ET opening in normal subjects and subjects with ET dysfunction and
patulous ET (McDonald 2012). A discrete air bolus was observed in normal subjects, but not subjects with ET dysfunction. The size of the bolus was also noticeably larger in the patients with patulous ET. The study also revealed insights which may explain some failures of endoscopic interventions. Opening at the pharyngeal orifice appeared normal in two of three subjects with ET dysfunction. Laser ablation of the pharyngeal orifice as described recently (Poe 2003) would likely not be beneficial in these two patients; preoperative assessment could identify such patients and the operative plan could be modified accordingly. A quantitative, objective clinical assessment would be valuable in determining whether these procedures are effective and, if so, how they could be modified to optimize results. Imaging methods may offer one feasible modality of evaluating ET function and the effects of ET interventions.

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APPENDIX

A. EXCISED LARYNX BENCH APPARATUS

All experiments were conducted using the excised larynx bench apparatus. As there is no innervation to the excised larynx, arytenoid, and thus vocal fold, position must be controlled mechanically. We use three-pronged “micrometers,” or micromanipulators to control arytenoid position (figure 1). These are inserted from a lateral approach and mimic the function of the

![Figure 1. Control of vocal fold position during excised larynx experiment. The arytenoids are controlled using two three-pronged devices which stabilize the lateral arytenoid and medialize the vocal folds. Anteriorly, a suture is placed through the midline thyroid cartilage and used to control vocal fold elongation (thin white arrow, lower left image). In the lower right image, the left arytenoid is not being adducted (thick white arrow) and unilateral vocal fold paralysis is simulated.](image-url)
adductory muscles. Vocal fold elongation is controlled via a third device connected via a suture to the thyroid cartilage.

**B. DIFFERENCES BETWEEN CANINE AND HUMAN LARYNX**

All studies described in this proposal used canine larynges. Larynges used in the studies included in this dissertation were harvested from mongrel dogs sacrificed for unrelated purposes. Historically, canine larynges have been used frequently in studies of phonation (Kakita 1981; Slavit 1991; Durham 1987). The differences between the canine and human larynx are detailed by Titze and explained here (Titze 2000). The canine does not have a clearly defined vocal ligament (Hirano 1974). It has a more prominent superficial layer of the lamina propria with nonexistent intermediate and deep layers. Dogs are able to initiate phonation but have difficulty sustaining it, possibly because the vocal ligament facilitates generation of the longitudinal tension needed to maintain high pitches. This vocal fold structure and corresponding phonatory tendencies are suitable for dogs, which produce bursts of phonation in the form of barks.

**C. MECHANISM OF ANTERIOR ARYTENOID ADDUCTION**

Gore-Tex suture attached to curled wire is passed through the thyroid cartilage or cricothyroid membrane via a guide needle. Once at the

![Figure X. Anterior AA with Voice Restoration Device (VRD). 1: small opening is created in thyroid cartilage. 2: VRD is passed through opening and hook is secured to soft tissue surrounding arytenoid. 3: tension on suture rotates arytenoid. 4: arytenoid is now in phonatory position. Image courtesy of Dr. Timothy McCulloch and included with his permission.](image-url)
muscular process of the arytenoid (confirmed by visualization of arytenoid movement), the
hook-wire apparatus is pushed through the guide needle and “hooked” on the soft tissue
surrounding the muscular process. A secure attachment is confirmed by visualization of
arytenoid rotation when tension is placed on the suture. If the hook did not catch, it can be
retracted and the process repeated. A schematic representation of this process is provided in
figure 3.

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