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Reliability of Subjective Endoscopic Parameters in the Differentiation of Essential Voice Tremor and Adductor Spasmodic Dysphonia Using High-Speed Videoendoscopy

Lindsey A. Parker
Louisiana State University and Agricultural and Mechanical College

RELIABILITY OF SUBJECTIVE ENDOSCOPIC PARAMETERS IN THE DIFFERENTIATION OF ESSENTIAL VOICE TREMOR AND ADDUCTOR SPASMODIC DYSPHONIA USING HIGH-SPEED VIDEOENDOSCOPY

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Lindsey Ann Parker
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ABSTRACT

Certain neurogenic voice disorders present with similar or overlapping audio perceptual voice characteristics. Developing reliable and standardized perceptual measures of vocal fold vibratory characteristics for such voice disorders can enable accurate diagnosis and lead to faster, targeted treatment. In this study, subjective perceptual vocal fold vibratory characteristics and the presence and absence of supraglottic events during phonation were investigated to differentiate between Adductor Spasmodic Dysphonia (ADSD) and Essential Vocal Fold Tremor (EVT) using high-speed videoendoscopy (HSV). The specific aims of the study were to 1) assess which subjective endoscopic vocal fold vibratory measures differentiate EVT from AdSD; and 2) assess the inter-rater and intra-rater reliability of the ratings.

High speed video recordings of vibratory vocal fold motion were selected to conduct a retrospective analysis on existing data. The participants were classified into three groups: 16 participants with a diagnosis of Adductor Spasmodic Dysphonia, 8 participants with a clinical diagnosis of Essential Vocal Tremor, and 10 participants with a diagnosis of Both (AdSD with Tremor). The inclusion criteria for HSV data was the presence of a full view of true vocal folds and supraglottic structures during vibration. It was hypothesized that HSV vocal fold vibratory measures and supraglottic events would distinguish EVT and ADSD and these measures would be reliable. In addition, the vocal fold vibratory features would be more reliable than supraglottic events in differentiating between the groups.

Results demonstrated mixed reliability for supraglottic and vocal fold vibratory parameters. None of the hypothesized supraglottic parameters demonstrated any significant distinction between diagnostic groups given the three raters’ responses. While all four vocal fold vibratory parameters revealed distinctive patterns between the three diagnostic categories, only

two, right/left TVF symmetry and anterior/posterior TVF symmetry, met the requirements for both reliability and differentiation. For these parameters, EVT demonstrated greater vocal fold symmetry in comparison to AdSD; however, those with a differential diagnosis of both demonstrated the highest vocal fold symmetry.

CHAPTER 1. LITERATURE REVIEW

Our voice is a vibrant component of our identity. The quality of its function not only shapes our projected image of ourselves, but also serves as a cornerstone for self-expression and our communication with others. A change in our voice can disrupt this ease of communication, introducing new stressors to daily lives. Dysphonia arises from an abnormality of the physical structures of the larynx, neurogenic anomalies, disease, or environmental causes which in turn affect the function of voice production (American Academy of Otolaryngology-Head and Neck Surgery, 2005). With abnormal production or an absence of voice, changes arise in vocal quality, pitch, loudness, resonance, and duration, leading to voice disorders (American Speech-Language-Hearing Association, 1993). Such disorders can range from a mild hoarseness to a complete loss of voice. While the most obvious consequences result in physical deficits of the larynx or a different perceptual voice quality, voice disorders wield a profound influence on a person's ability to communicate, affecting their functional activities, emotional status, professional potential, and their overall quality of life (Ma & Yiu, 2001).

The sooner a voice disorder can be identified, the sooner targeted treatment may begin. Challenges in assessing aperiodic voice disorders with current measures due to varying severity, overlapping perceptual characteristics, and unknown etiologies can lead to a delayed diagnosis or even misdiagnosis, less effective treatment management, and prolonged confusion and frustration for the patient. Expediency in diagnosis supports efficient treatment and management of a voice disorder to minimize the emotional, social and financial toll for the individual. Developing accurate and reliable parameters to differentiate characteristics for easier identification is essential to this practice. The goal of this study is to enhance the known literature on the differential diagnosis of Adductor Spasmodic Dysphonia (AdSD) and Essential Voice Tremor (EVT) by investigating if the identified parameters are both reliable and distinct.

Voice Disorders

Voice disorders take a larger role in our lives than one might realize. With an estimated prevalence of approximately 6% of the general population, voice disorders pose a significant problem, requiring proper diagnosis and treatment (Roy, Merrill, Gray & Smith, 2005). Voice disorders can occur throughout the lifespan. The largest epidemiologic study for prevalence conducted by Roy et al. (2005) found that approximately 30% of the adults surveyed reported experiencing voice problems at some point in the past. Those with respiratory allergies, asthma, frequent colds and sinus infections exhibit a higher likelihood of developing a voice disorder (Roy, Merrill, Thibeault, Parse, Gray & Smith, 2004). Women also show higher lifetime prevalence for voice disorders, with higher prevalence for chronic disorders lasting longer than a month (Roy et al., 2005). Results from Roy et al. (2005) identified four variables that increase a person's risk for a voice disorder: age (between 40 and 59 years), gender (female), level of education (16 years or greater), and a family history positive for voice disorders.

Complicated etiologies and controversies within the field over diagnostic definitions can make the differential diagnosis of voice disorders particularly difficult. Such discrepancies reflect the ever-changing nature of the field and our understanding of voice production (Verdolini, Rosen & Branski, 2006). Different clinicians and doctors use different models to examine results and often pull from subjective experiences which naturally vary in definition and application, leading to the current quagmire of clinical diagnosis. Having standardized, accepted parameters to distinguish between pathologies leads to targeted treatment and promotion of the best possible care and health for the people with these voice disorders. If clarity is ever to be achieved, better models and parameters with agreed upon guidelines for distinguishing between voice disorders must be established.

The literature review examines two such voice disorders steeped in conflicting, overlapping perceptual characteristics, Essential Voice Tremor and Adductor Spasmodic Dysphonia, and discusses the suitability of high-speed laryngeal imaging for the development of definitive, reliable parameters for the differentiation of these two voice disorders.

Essential Voice Tremor (EVT)

Essential Voice Tremor is a chronic voice disorder characterized by the perception of an unsteady voice due to involuntary, rhythmic muscle movements. EVT falls within the broader spectrum of essential tremor, one of the most common movement disorders (Gamboa et al., 1998). Such tremor stems from the periodic contraction of muscles in an alternating or synchronous pattern; distinguished by the rate and magnitude of oscillation of these muscles (Warrick, Dromey, Irish, & Durkin, 2000; Lester, Barkmeier-Kraemer, Story, 2013). While a degree of tremor falls within everyone’s normal limits of function, abnormal tremor such as essential tremor presents with larger amplitudes, a lower frequency range, and may interfere with purposeful movement (Colton et al., 2011). EVT mirrors essential tremor’s absence at rest and potency while maintaining a particular posture during voluntary (kinetic) movement, such as voicing (Colton et al., 2011; Sulica & Louis, 2010).

Essential voice tremor can affect the muscles of the larynx, the pharynx, the palate, the hypoglossus of the tongue, the strap muscles, and respiratory muscles (Sulica & Louis, 2010; Anand, Shrivastav, Wingate, Chheda, 2012; Lundy, Roy, Xue, Casiano, Jassir, 2004; Lester & Story, 2013). Physiologically, this presents in the rhythmic oscillation of the involved structures. This periodic rhythm in the muscles creates tension in the vocal folds, leading to the changes in fundamental frequency and in the force of vocal fold adduction. These fluctuations in the force of adduction create variations in the subglottal air pressure, affecting vocal intensity. Others perceive this modification of the fundamental frequency and intensity as an unsteady voice (Colton et al., 2011). This salient feature of a perceptual periodic, tremulous voice in the absence of rigidity, spasm, and bradykinesia for involuntary movement, marks a differentiating characteristic in diagnosis (Warrick, et al., 2000; Sulica & Louis, 2010). However, in severe cases, the force of adduction may become great enough to completely stop voice production, producing voice stoppages that mimic characteristics common to adductor spasmodic dysphonia (AdSD) (Lundy, 2004).

A heterogenetic disorder, EVT exhibits variable severity and presentation. Prevalence estimates for essential tremor range between 0.4% to 5.6% of the population over 40, with EVT presenting in approximately 18-30% of clinical cases, and with one study estimating it as high as 62% (Warrick et al., 2000; Lester et al., 2013; Sulica & Louis, 2010). Evidence indicates a hereditary link, with up to half of patients with essential tremor having a similarly affected family member (Colton et al., 2011; Sulica & Louis, 2010). The etiology of essential tremor and EVT remains controversial within the field, with suggested influence ranging from the inferior olivary nucleus, dysfunction of the cerebellum, extrapyramidal system, to the olivocerebellar tracts within the central nervous system (Warrick et al., 2000; Colton et al., 2011).

Patients with EVT generally report a gradual onset, which mirrors the slow progression of essential tremor (Colton et al., 2011). EVT presents most frequently in the 7th decade of life (Colton et al., 2011; Sulica & Louis, 2010). However, further research with a wider survey of the population, as suggested by Sulica and Louis (2010), suggests a bimodal distribution with a smaller number of cases beginning earlier, with a mean onset of 45.3 years (Warrick et al., 2000). Although an early study by Larsson and Sjogren (1960) found essential tremor more common in men, Koller, Busenbark & Miner (1994) demonstrated a more equal gender distribution, where 49% were women and 51% were men (Colton et al., 2011; Sulica & Louis, 2010). In contrast, EVT develops more often in women than men, with women representing more than 80% of cases (Sulica & Louis, 2010). This skewed statistic, however, may be attributed to selection bias based upon who seeks clinical treatment.

In order to detect EVT in its pure form, one must first understand how it presents across different metrics. The involuntary, rhythmic oscillation of the laryngeal muscles involved in speech produce can alter the perceptual sound of the voice. This periodic modulation of the frequency or intensity of a person's voice is most noticeable during prolonged vowel phonation and can also be detected in contextual speech (Colton et al., 2011). Perceptual voice characteristics of EVT include changes in pitch level, monopitch, voice tremor, harshness, characteristic strain/struggle, and in the most severe cases voice stoppages and breathiness (Colton et al., 2011; Lundy et al., 2004). People with EVT may complain of a shaky voice, decreased intelligibility, and of others' misconceptions regarding their emotional state due to the tremulous quality of their voice (Sulica & Louis, 2010; Colton et al., 2011; Lester et al., 2013).

Analysis of the acoustic signal of a person's speech can offer indirect, objective data to separate EVT from the normal levels of tremor found in the general population. Everyone has a normal degree of modulation of intensity and frequency in his or her voice as they speak. Those with EVT demonstrate an atypical level of changes due to the characteristic abnormal physiologic oscillations with an acoustic signal between 4-7 Hz (Lester & Story, 2013; Sulica & Louis, 2010; Anand et al., 2012; Gamboa et al., 1998). This tremor rate can present with slight variations based upon the anatomical structures affected (Dromey, Warrick, & Irish, 2002). The analysis of these modulations and the relationship between the mean differences in the modulation between frequency and amplitude has been found to distinguish between normal voices, vibrato, and those who present with vocal tremor (Winholtz & Ramig, 1992).

Through laryngoscopy, the rhythmic movement of one or more affected laryngeal and pharyngeal structures can be directly observed during phonation and/or at rest (Colton et al., 2011). Having this direct method of observation offers distinct benefits from other methods in regards to the perceptual detection of this rhythmic oscillation. Although Colton et al. (2011) claimed that the people with essential tremor demonstrate normal structure and movement, results from Sulica & Louis (2010) challenged that assertion, specifically in regards to such movement; showing evidence of global involvement for laryngeal structures in contrast to other vocal disorders through laryngoscopy.

The heterogenetic nature of EVT's presentation can cause complications in clinical diagnosis. Tremor can exhibit symptoms mild enough to go unnoticed in over 50% of cases, and yet at its most severe it can present with sharp vocal stoppages that are not generally attributed to EVT (Sulica & Louis, 2010). Determining vocal involvement for essential tremor is equally difficult, with variable rates of incidence produced by discrepancies between examiners in identifying perceptual acoustic signs of tremor (Sulica & Louis, 2010).

Standards of diagnosis for EVT rely on subjective and indirect measures with a degree of human error, leading to misdiagnosis and improper and insufficient treatment. Clinicians and doctors traditionally form their clinical judgment in the diagnosis of EVT without laryngoscopy, designated instead on the basis of perceptual acoustic evidence of tremor in the voice and a case history (Sulica & Louis, 2010; Anand et al., 2012). In the literature, Sulica and Louis (2010) reported that visualization of the affected laryngeal structures remained largely absent from papers discussing EVT. Perceptual acoustic measures have their place in diagnosis; however, they remain an indirect, subjective measure of the actual physical laryngeal function. The lack of reliability of these subjective measures can make it difficult for clinicians to distinguish EVT from other disorders when it does not present as a clear case and can increase the likelihood of improper diagnosis.

Adductor Spasmodic Dysphonia (AdSD)

Spasmodic dysphonia is a rare, chronic voice disorder characterized by the perception of uncontrolled voice breaks and marked effort during speech due to involuntary spasming of the laryngeal muscles (Ludlow et al., 2008; Tanner, Roy, Merrill, Sauder, Houtz & Smith, 2012). This muscle spasming can adversely affect a person's functional communication by disrupting the vibratory movement of the vocal folds and the movement of the surrounding structures. Spasmodic dysphonia divides into two subtypes: adductor spasmodic dysphonia (AdSD) and abductor spasmodic dysphonia (AbSD). While they usually present separately, a few documented cases of simultaneous adductor and abductor spasms in the same patient do exist (Ludlow et al., 2008). Occurring in 75-80% of cases, AdSD is marked by irregular closing of the vocal folds during speech (hyperadduction) due to spasmodic bursts of the laryngeal adductor muscles which produce voice breaks with a strained, strangled voice quality (Orbelo et al., 2014; Colton et al., 2011; (Patel, Liu, Galatsanos, & Bless, 2011). Less common, AbSD is characterized by uncontrolled opening of the vocal folds (hyperabduction) during connected speech, in particular with voiceless consonants and followed by whispered speech segments (Ludlow et al., 2008; Colton et al., 2011).

Patients with spasmodic dysphonia typically report a gradual onset, with the severity of voice problems fluctuating over time; many reaching a plateau with a smaller set progressing worse or getting better, but never resolving (Tanner, Roy, Merrill, Sauder, Houtz & Smith, 2011a; Tanner, Roy, Merrill, Sauder, Houtz & Smith, 2011b ; Colton et al., 2011). However, in an epidemiological survey conducted by Tanner, et al. (2011a,b) a small subsection of those diagnosed experienced a sudden, rather than gradual, onset of symptoms. With the most common time of onset during the fifth decade, the voice disorder is more frequently found in women, approximately 60-85% of cases (Tanner et al., 2011a, Tanner et al, 2011b; Ludlow et al., 2008). Despite its infrequent occurrence in the clinical population with an estimated prevalence of 1 in 100,000, Colton et al. (2011) noted that spasmodic dysphonia has received much attention in the literature.

Though once linked to psychopathic and emotional disturbances, current literature considers AdSD a focal laryngeal dystonia. A neurological movement disorder of the central nervous system, it is characterized by uncontrollable muscle contractions that affect the laryngeal muscles (Patel et al., 2011; Colton et al., 2011; Ludlow et al., 2008). Dysfunction appearing during the execution of a task and remaining largely unseen at rest marks a salient feature of focal dystonias (Colton et al., 2011). These spasmodic contractions that occur during speech may be in response to misprocessed afferent information triggered by variation in air pressure during phonation (Colton et al., 2011).

Like EVT, the pathophysiology and epidemiology of AdSD requires further research. Through the compilation and analyses of case history, researchers have identified certain risk factors associated with spasmodic dysphonia. These include a higher personal history of mumps, blepharospasm (involuntary closing of the eyelids), tremor, rigorous voice use, and a family history of voice disorders along with an extended family history of tremor and cancer compared to the control group (Tanner et al., 2012). Other neurological signs which co-occur with AdSD include: hyperreflexia, torticollis, and vocal, jaw, and facial or limb tremor (Colton et al., 2011). Due to these links with other neurological disorders, determining the locus of the disorder remains difficult, however, the literature suggests potential involvement with the basal ganglia, sensorimotor cortex, thalamus, or cerebellum (Colton et al., 2011; Isetti, Xuereb, & Eadie, 2014).

The intermittent, spasmodic bursts of muscle movement during speech production that define AdSD alter the perception of a person's voice and disrupt effective communication. This spasming of the laryngeal muscles leads to more effortful speech. Of note, such muscle bursts do not tend to present while whispering (Isetti, Xuereb, Eadie, 2014; Ludlow et al., 2008). The amount of effort required for speech correlates with severity. The characteristic perceptual signs of the voice disorder include the struggle and strain to talk along with the intermittent voice stoppage and voice breaks (Colton et al., 2011; Patel et al., 2011; Barkmeier et al., 2001). These frequent voice breaks generally occur during the production of voiced speech sounds (e.g. /z/, /g/, /b/) and can be denoted during conversational speech and sustained phonation in moderate to severe cases (Barkmeier et al., 2001). Depending on the severity of presentation, people may demonstrate levels hoarseness or harshness of voice, strain/struggle, a sudden interruption of voicing, increased tension, loudness and pitch variations, and pitch breaks (Colton et al., 2011).

Patients may report their symptoms reduced or absent altogether during certain activities such as laughing, coughing, clearing one's throat, humming or talking in falsetto; while stressful speaking situations can exacerbate the effects (Barkmeier, Case, Ludlow, 2001). This choked voice lends to impressions of a shaky, cracking or tremulous quality, which people complain others perceive as overly emotional (Isetti et al., 2014; Colton et al., 2011). In rarer cases, AdSD can also present with perceptual characteristics similar to an aging voice including breathiness, aperiodicity, vocal fry and vocal tremor (Isetti et al., 2014).

The pronounced spasms and aperiodic bursts of hyperactivity associated with AdSD have noticeable effects on the acoustic signal. The added force of the vocal folds slamming together requires greater pressure than normal to force the vocal folds back apart during speech, increasing resistance and the effort required to speak with a more strained vocal quality (Colton et al., 2011). Intermittent instigation of the voice breaks and stoppages produce wide variations in a person's fundamental frequency. This is supported by a 1988 study by Davis et al., who found that people with spasmodic dysphonia exhibited a greater variation of fundamental frequency while reading a passage when compared to normal controls (Colton et al., 2011). While recent research has attempted to characterize acoustic parameters for AdSD, Patel et al. (2011) found that the aperiodicity of acoustic signals in more severe voice dysfunctions led to less reliable and valid data, in part due to the indirect nature of the measurements, which can reflect greater variance in speech production (Barkmeier et al., 2001).

Laryngeal imaging offers clinicians a critical visual component towards diagnosis that indirect acoustic and perceptual methods cannot (Patel et al., 2011). While the anatomical structure of the larynx appears normal in those with AdSD, phonation reveals the hyperadduction of the vocal folds fundamental to the disorder (Ludlow et al., 2008; Colton et al., 2011). Through laryngoscopy, further reports revealed a variation in effects from the appearance of bowed vocal folds, quick adductory movements of the true vocal folds, ventricular (false vocal) folds and supraglottal structures, to small irregular movement of the true vocal folds to periodic laryngospasm in some clinical cases (Colton et al., 2011). Full stoppage of voice has been reported to occur due to the adduction of the true vocal folds, tremor, or the ventricular folds

(Colton et al., 2011). Ludlow et al. (2008) found that direct visualization supported perceptual acoustic parameters; with the identification of normal vocal fold movement during respiration, coughing, throat clearing, and whistling and spasms observed during prolonged vowels and during sentences.

Challenges & Considerations for Differential Diagnosis and Reliability

The severity and heterogenic presentation of EVT and AdSD create challenges for clinical diagnosis. Not only can tremor and AdSD co-occur, the strain, strangled, and tremulous vocal qualities that characterize these disorders frequently sound similar to raters (Ludlow et al., 2008; Lundy et al., 2004). This is exacerbated by the nature of severe presentations of EVT and AdSD which can present with symptoms that mimic hallmarks of the other disorder, such as of voice stoppages with EVT and tremor co-occurring with AdSD. Both can also demonstrate improvement with alcohol (Sulica & Louis, 2010). Some form of vocal tremor accompanies AdSD in approximately 26% of cases; displaying what some argue to be periodic fluctuations in pitch or loudness during sustained phonation (Tanner et al., 2011a; Tanner et al., 2011b; Tanner et al, 2012; Barkmeier et al., 2001), while other patients report to display an irregular tremor similar in rate to EVT (Isetti et al., 2014; Sulica & Louis, 2010).

A more thorough documentation of a person's case history and knowledge of concomitant factors, careful attention to auditory and visual perceptual symptoms, and ascertaining the response to treatment together may provide a more accurate diagnosis. This diagnosis process, however, can be muddled by complex presentations between EVT and AdSD.

While people who present with AdSD and vocal tremor combined follow a similar trajectory for their voice symptoms to those with AdSD, some distinctions were observed. The AdSD subjects who also exhibited vocal tremor (SD plus tremor) were on average significantly older at 64.1 years, compared to those with AdSD alone at 59.7 years (Tanner et al., 2011a; Tanner et al., 2011b). In their study, Tanner et al. (2011a,b) also noted that 56% of those with coexisting symptoms also reported greater success in treatment via medication to treat their voice problems compared to just 21% diagnosed with AdSD. Those with EVT typically present later in life compared to those with AdSD and they are also more likely to report incidence of tremor in the family history (Sulica & Louis, 2010).

On a day to day basis, symptoms of EVT remain even and do not change with sensory tricks or phonemic composition, while symptoms of AdSD are more dynamic, waxing and waning over time and demonstrating improvement through such acts as laughing, singing, shouting, and whispering (Sulica & Louis, 2010; Ludlow, 2012). In a study by Lundy et al. (2004), those with tremor could be differentiated via the intensity of the tremor (Matr) and the frequency variability. Through laryngeal imaging, one can distinguish that people with EVT do not demonstrate the same sphincteric glottis closure of AdSD, but do exhibit global involvement of the laryngeal structures (Sulica & Louis, 2010). In a comparison study by Ludlow et al. (2008) comparing perceptual signs, AdSD demonstrated higher ratings for shouting being less affected than speech, a higher mean number of adductor voice breaks in sentences and functional vocal fold asymmetry during speech, while those with EVT exhibited higher ratings for laughter and whisper less affected than speech, and a higher presence with voice tremor during prolonged vowels. A person’s response to Botox treatment may also lend in diagnosis. While both AdSD and EVT are treated by Botox injections, people with EVT report lower success rates of 50-65% compared to 90% of people with AdSD, along with a higher incidence of side effects (Orbelo, et al., 2014; Ludlow et al., 2008; Tanner et al., 2011a; Tanner et al., 2011b).

The aperiodic nature of the speech signals for severe cases also creates challenges in analysis using acoustic or stroboscopic means given human and instrument limitations (Patel et al., 2011). While acoustic analysis has differentiated normal subjects from AdSD and those with EVT, such analysis has not been successful in differentiating spasmodic dysphonia from essential vocal tremor (Lundy et al., 2004).

Despite extensive documentation of the disorders, standards for differentiating AdSD from EVT remain incomplete, leading to an overlap of diagnosis. While the literature considers the highest priority of the field to characterize AdSD and identify risk factors, indistinct symptoms remain without set standardized methods for clinicians to approach proper identification and description (Ludlow et al., 2008; Barkmeier et al., 2001; Orbelo et al., 2014). In an effort to change this, The Dystonia Coalition in partnership with research institutions endeavored to establish the Structure of Spasmodic Dysphonia–Diagnosis and Assessment Procedure (SD-DAP) for speech and nasoendoscopy recordings to be rated by speech-language pathologists, neurologists, and laryngologists at voice centers in comparison to onsite diagnosis of patients (Ludlow, 2012).

The reliability of perceptual judgments, however, presents additional challenges in establishing differential diagnosis. The initial findings of the Dystonia Coalition revealed poor reliability between the raters for both speech and nasoendoscopy recordings even after training, with 30% agreement for speech and 50% agreement on diagnosis for nasoendoscopy (Ludlow, 2012). Raters between and within these sites did not agree on the best diagnosis. Thus, it is critical to fill this gap in the research in order to properly identify and treat people with voice disorders. However, in a systematic review of the literature for stroboscopy, only 11 of the 80 articles which met the inclusion criteria reported reliability for the subjective perceptual ratings

(Bonilha, Focht, Harris-Martin, 2015). Out of the articles Bonilha et al. found, two reported good inter-rater and intra-rater reliability (2015). This lack of rigor in the methodology and poor reporting of the reliability reveals a gap in the research.

While current clinical assessment incorporates case history and laryngeal imaging (videostroboscopy), perceptual judgments of the voice remain the standard for differentially identifying individuals with AdSD from other vocal disorders such as EVT (Barkmeier et al., 2001). Standardized methods and descriptions are needed for all levels of assessment--for many symptoms of AdSD appear similar to those of EVT or muscle tension dysphonia (Barkmeier et al., 2001). This lack of accepted standards can lead to misdiagnosis and prolonged stressed for the patient with delayed or inappropriate treatment. One effort to develop perceptual speech symptom protocol by Barkmeier et al. (2001) focused on vowel breaks, breathy breaks, and tremor breaks, to distinguish between perceived symptoms of AdSD, AbSD, and EVT. While effective, these measures remain indirect, subjective and prone to human error. Patel et al. (2011) reported direct visualization of the vocal folds through laryngeal imaging to demonstrate potential to eliminate errors due to indirect observation. In a review of the literature, Ludlow et al. (2008) identified a three-tiered approach to screen for AdSD, with laryngoscopy used for a definitive diagnosis. Adoption and standardization for laryngeal imaging, however, has proved slow to gain traction. Greater consensus must be achieved within the field in determining hallmarks of the disorder.

Laryngoscopy can offer critical information on the physical laryngeal structures affected by these two voice disorders. However, as of yet, no established parameters for stroboscopic signs of EVT or AdSD exist (Colton et al., 2011; Deliyski & Hillman, 2010; Mendelsohn, Remacle, Courey, Gerhard, Postma, 2013). Laryngeal imaging is considered to be limited in clinical evaluation in part due to the difficulty of tracking fundamental frequency within the current parameters of imaging quality for videostroboscopy (Colton et al., 2011). More recent studies have included detailed endoscopic examination of the vocal folds and surrounding laryngeal structures with the aim to establish such standards (Sulica & Louis, 2010; Inwald, Dollinger, Schuster, Eysholdt, Bohr, 2011; Lester et al., 2013).

Technical advancements in high-speed videoendoscopy (HSV) may allow for greater distinction in the future, capturing movement disruptions from involuntary spasms or muscle imbalance in severe cases of EVT and AdSD that other techniques cannot (Patel et al., 2011). The adoption of high-speed videoendoscopy for clinical diagnosis may offer the standardized parameters that the field requires in order to offer tailored treatment based upon accurate diagnosis.

Laryngeal Imaging

For the clinical practice, investigation of the true vocal fold vibratory patterns can be accomplished using videostroboscopy, videokymography, and high-speed videoendoscopy (Deliyski & Hillman, 2010; Kunduk, Yan, McWhorter, Bless, 2006). While it is important to factor in vocal quality and a through case history, visualization is an essential component of a complete diagnostic protocol (Mendelsohn et al., 2013; Deliyski & Hillman 2010). Imaging can provide a definitive answer based upon previous information gathered and offer new insight on laryngeal function.

Videostroboscopy

Videostroboscopy stands as the current gold standard of evaluation of the vocal fold function. It offers a real time examination of the vocal folds and provides a visual estimate of the vibratory function of the vocal folds (Mehta, Deliyski & Hillman, 2010; Deliyski & Hillman

2010; Mehta & Hillman, 2012a; Deliyski, Petrushev, Bonilha, Gerlach, Martin-Harris, Hillman, 2008). Videostroboscopy allows clinicians to observe dynamics of vocal fold vibration that halogen light laryngoscopy cannot; providing real time assessment of the vocal fold mucosal wave (Deliyski & Hillman, 2010; Mendelsohn et al., 2013). This technique of synchronized flashing light provides several advantages over other methods. It allows for automatic visualization of the larynx and surrounding structures with simultaneous audio playback, good image quality, and also affords clinicians the ability to record long sections with standardized rates of compression and archiving measures for data storage (Deliyski & Hillman, 2010).

Limitations in the nature of how stroboscopy functions, however, presents challenges in diagnosis for aperiodic voice disorders. The very synchronization of light that lies behind the technology relies upon a voice with a steady, reliable fundamental frequency; a characteristic many voice disorders do not embody (Mendelsohn et al., 2013). Rather than capture each open-close cycle of vocal fold vibration, stroboscopy constructs its images from quasi-periodic voice signals (Deliyski & Hillman, 2010). Stroboscopy creates its characteristic slow motion illusion by splicing together different phases of the glottal cycle across multiple cycles to stand for the whole. It does not represent, therefore, a true projection of the vocal fold movement. This editing relies upon the pitch tracking from the laryngeal microphone to predict the next glottal cycles and makes assumptions in its selection based on a consistent glottal period (Deliyski et al., 2008). Aperiodic phonation disrupts this process, desynchronizing the strobe light from the actual phase of vocal fold movement; limiting its ability to classify such disorders with blurred, indistinct representation of phonatory vibration (Deliyski et al., 2008; Mendelsohn et al., 2013; Deliyski & Hillman, 2010). Stroboscopy also requires a minimum phonation time of 2 seconds to adequately condense the information it collects, constricting its applicability for those not only with irregular phonation, but also limited duration of speech (Mendelsohn et al., 2013).

As a result, stroboscopy can provide clinicians little information on disorders such as EVT and AdSD which do not follow the necessary modular movement required. Milder cases of AdSD can, in fact, present a significant challenge, given that the unaided eye often cannot determine aperiodic vocal fold motion (Sulica & Louis, 2010). This limitation creates holes in diagnostic potential, for without the ability to reconstruct a slow motion view of the vocal fold vibratory cycles clinicians cannot accurately determine the dysfunction by stroboscopy alone (Deliyski & Hillman, 2010). Thus with stroboscopy, more subjective, indirect measures must still be utilized to conceptualize a disorder and a potential solution for treatment.

High-Speed Videoendoscopy

High-speed videoendoscopy (HSV) stands poised as a possible solution to the problems stroboscopy presents. While the development of high-speed imagery lagged behind stroboscopy for commercial clinical use, high-speed films have been used to study vocal fold motion for decades (Deliyski et al., 2008). Farnsworth conducted the first documented research on slow motion capture of the vocal folds with a high-speed camera through Bell Laboratories in the late 1930s (Deliyski et al., 2008; Mehta & Hillman, 2012b). Advancements in recent years in lighting with the use of rigid and flexible endoscopic cameras and image quality paved the way for better quality laryngeal high-speed videoendoscopy (Mehta & Hillman, 2012b). HSV by default allows the clinician better observation of the full glottal cycle without editing and condensing the visual information. By capturing at minimum 2000 frames per second (fps) of the vocal folds, HSV obtains 10-20 frames for each open close cycle depending on fundamental frequency and negates the need for consistent periodic fundamental frequency for adequate capture of the motion of the vocal folds (Mendelsohn et al., 2013). As a result, HSV offers the potential to become a useful analytic tool for clinicians to diagnose severe cases dysphonia and aperiodic voice disorders.

While videokymography, a technique which analyzes movement via multiple images of the vocal folds along a fixed, single horizontal line, also allows clinicians to view the true vibratory characteristics of the vocal folds, HSV examines the full length of the vocal folds for a more complete picture (Deliyski et al., 2008; Deliyski & Hillman, 2010, Kunduk et al., 2006). Utilizing HSV, clinicians can observe more transient vocal behaviors such as phonatory breaks, laryngeal spasm, the onset and offset of phonation, and rapid laryngeal movements such as vocal attack, coughing, throat clearing, and laughing (Deliyski & Hillman, 2010). This is especially useful for distinguishing between voice disorders such as EVT and AdSD, where the distinction between such actions could produce clearer evidence for differential diagnosis.

Through technical advancements, HSV evolved to become a possible clinical tool to investigate vocal fold vibratory function. Recent studies demonstrate a clinical benefit for utilizing HSV over videostroboscopy (Inwald et al., 2011; Patel et al., 2008). Inwald et al. (2011) evaluated the laryngeal mechanism based upon parameters that measured the mucosal wave, glottal closure, and vibratory amplitude. Use of this also improved correlation in the diagnosis of presbyphonia which requires better visualization of minute vocal fold atrophy (Mendelsohn et al., 2013). In one case, HSV required less investigation time, caused fewer methodological mistakes and was more reliable for detecting deficits when compared to stroboscopy (Inwald et al., 2011). Others, however, have argued over the practicality of switching to HSV over stroboscopy. Mendelsohn et al. (2013) found no benefit between the two imaging techniques in distinguishing vocal fold polyps and concluded similar outcomes between the two for the diagnosis for non-neurologic disorders. High speech videoendoscopy, however, may better serve in filling clinical gaps for severe and aperiodic voice disorders where current stroboscopy analysis cannot match (Patel et al., 2008). The significance in the difference between analysis with HSV and stroboscopy largely depends on the type of voice disorder analyzed.

While HSV offers great potential in the field as a replacement for videostroboscopy, it faces further challenges before becoming the preferred observation method in the field. No clear standards for HSV exist and consensus within the literature to establish such parameters remains divided (Mendelsohn et al., 2013; Deliyski & Hillman, 2010; Deliyski et al., 2008). Without clear justification for the cost of additional equipment or definitive norms, many hold off in its use--thus perpetuating a clinical reluctance in adoption. HSV also requires greater consideration for storage, commanding more space in exchange for more detailed imaging. Researchers contend over the most appropriate compromise in frame rate, balancing between storage capabilities and accurate rendering. Shaw and Deliyski (2008) found that specific analysis of the mucosal wave captured at 2000 fps proved insufficient with high frequency. For this particular study, this does not present a concern due to the selection of the subjective characteristics observed.

In clinical practice, many interpret HSV via subjective visual analysis. While this sort of analysis can provide useful observations, it remains a fallible technique subject to the impressions and individual ratings of a particular clinician or doctor. Standardized objective measures may solve this dilemma; offering accurate analysis for differential diagnosis without subjective parameters which vary among individuals. However, until rigorous objective measures can be developed and tested, the clinical relevance of its use remains sparse. Paired with a thorough case history and clinical observation, HSV provides potential for advancement in diagnosis and developing better treatment; especially for voice disorders with neuromuscular etiologies such as EVT and AdSD.

The literature to this point has not directly examined both EVT and AdSD together via high-speed videoendoscopy. Continued efforts by researchers utilized HSV to explore norms for normal voices (Ahmad, Yan, Bless, 2012a; Ahmad, Yan, Bless, 2012b; Bonilha & Deliyski, 2008; Bonilha, Deliyski, Gerlach, 2008; Kunduk et al., 2006; Kunduk, et al, 2010; Shaw & Deliyski, 2008), and to develop distinctions between normal and disordered voices (Patel et al., 2008; Mendelsohn et al., 2013). Studies also indicate potential for developing objective parameters for analyzing vocal fold movement via glottal width (Popolo & Titze, 2008), phonovibrogram wavelet analysis (Unger, Hecker, Kunduk, Schuster, Schick & Lohscheller, 2014) and glottal area segmentation (Pinheiro, Dajer, Hachiya, Montagnoli & Tsuji, 2014; Ikuma, Kunduk & McWhorter, 2014). Specific objective analysis of the vocal folds with the glottal area waveform provided a promising foundation for further pursuit of such objective parameters (Yan, Ahmad, Kunduk, Bless, 2005; Ikuma et al., 2014).

While previous research utilized subjective visual-perceptual parameters to establish vocal norms (Lester et al., 2013; Sulica & Louis, 2010), to differentiate disordered from normal voice populations (Inwald et al., 2011), to compare AdSD from muscle tension dysphonia (Patel et al., 2011), and examine the different effects of Botox for EVT and AdSD (Orbelo et al., 2014; Warrick et al., 2000), no studies have analyzed the two voice disorders using high-speed videoendoscopy.

Purpose of Current Study

The specific aims of the study were to assess the efficacy and reliability of subjective measures using HSV to differentiate essential voice tremor (EVT) from adductor spasmodic dysphonia (AdSD). It was hypothesized that 1) experienced raters would produce greater intra-rater reliability and 2) that HSV vocal fold vibratory measures and supraglottic events would distinguish EVT and ADSD and these measures would be reliable. In addition, the vocal fold vibratory features would be more reliable differentiating between the groups.

Based upon established visual laryngeal characteristics of laryngeal structure and movement defined by the Dystonia Coalition (Ludlow, 2012) and a review of the literature, it was hypothesized for supraglottic events that supraglottic activity during voice initiation, arytenoid twitch, and false vocal fold involvement would best suggest AdSD for supraglottic features; while the presence of pharyngeal tremor, arytenoid tremor, rhythmic supraglottic oscillation, and complete cessation of the true vocal folds would best suggest EVT. Intermittent false vocal fold adduction might be seen in the presentation of subjects with AdSD with Tremor (Table 1.1).

Table 1.1
Hypothesized Differentiations of Supraglottic Parameters

Diagnostic Group	Supraglottic Endoscopic Parameter
Voice Tremor	Pharyngeal Tremor
	Arytenoid Tremor
	Arytenoid Tremor Location
	Complete Cessation of TVF Vibration
	Presence of Rhythmic Supraglottic Oscillation
	Location of Rhythmic Supraglottic Oscillation
Adductor Spasmodic Dysphonia	Supraglottic Activity During Voice Initiation/Glottal Attack
	Arytenoid Twitch
	Supraglottic Activity During Sustained Phonation/Constant
	Severity of FVF Involvement
Both	Intermittent FVF Adduction/Involvement

Regarding vocal fold vibratory patterns, it was hypothesized that EVT would demonstrated rhythmic, symmetrical features based upon its characteristic rhythmic oscillations while AdSD would exhibit irregular, asymmetrical features given its characteristic intermittent spasms (Table 1.2)

Table 1.2
Hypothesized Differentiations of TVF HSV Parameters

High-Speed Videoendoscopy Parameter	Voice Tremor	Adductor Spasmodic Dysphonia
Regularity of Vibration	Regular	Irregular
Right/Left TVF Symmetry	Symmetrical	Asymmetric
Anterior/Posterior TVF Symmetry Of the Same Fold	Symmetrical	Asymmetric
Phase Symmetry	Symmetrical	Asymmetric

CHAPTER 2. METHODS

Participant Data Records

Video recordings of 34 patients were selected to conduct a retrospective analysis. Data were collected through Our Lady of the Lake Regional Medical Center (OLOL) over the past 5 years during routine clinical procedure and selected from the laryngeal imaging lab database maintained at Louisiana State University (LSU). The participants were classified into three groups. The first group consisted of 16 participants with a clinical differential diagnosis of AdSD. The second group consisted of 8 participants with a clinical differential diagnosis of Vocal Tremor. The third group consisted of 10 participants with a clinical diagnosis of both (AdSD with Vocal Tremor). All HSV observations were conducted by the same laryngologist at OLOL-Voice Center. The same laryngologist determined differential diagnosis for all participants. The use of the data in the study was approved by LSU, the LSU Health Science Center and OLOL Internal Review Boards.

HSV data were collected via a rigid 70° rigid laryngoscope (Model 9106, KayPENTAX) and paired with an HSV system (Model 9700, KayPENTAX) and a 300-watt cold light source (CLV-U20). Sustained phonation of /i/ at a steady, comfortable pitch and loudness was recorded with a sampling rate of 2,000 fps. Each video was digitally stored in the database at an uncompressed 8-bit monochrome grayscale with a pixel resolution of 120x256 pixels.

For this study, video recordings of each subject's vocal fold vibratory behavior during sustained /i/ were examined for visual perceptual subjective analysis. First, an initial overview of the supraglottic structures was observed at 200 fps playback rate, followed by observation of vocal fold vibratory function during sustained phonation at 10 fps playback rate with each HSV recording. No audio perceptual recordings or additional identifying information was included in the presentation of the videos.

These high speed video clips were selected by the same trained speech-language pathologist with experience treating voice disorders to ensure consistency. The given video segments were chosen based on the following inclusion criteria: sustained phonation present during the video segment, all frames had an unobstructed view of true vocal folds, the anterior commissure was present in the frames, adequate lighting was present to distinguish laryngeal structures, and the images were focused. This was to ensure video quality and continuity across selected segments.

Subjective Video Analysis

The HSV segments were rated by three individuals with different levels of experience, a trained speech-language pathologist specialized in voice disorders (experienced rater) and a graduate student and PhD student in speech-language pathology (inexperienced raters). Raters were blind to diagnosis and played video segments in a random order after a training session. Each rater assessed the selected video segments for the presence, partial involvement or absence of each parameter along with the location of any detected involvement (left, right, both, lateral, or anterior/posterior as determined) regarding the following subjective parameters for supraglottic events and true vocal fold vibratory features (see Appendix A for a description of each parameter).

The raters gave a score based upon the level of involvement and potential location in the assessment of the parameters for each subject; with each voice disorder adding to a total possible score (see Appendix B for the rating form). This offered a distribution of scores to describe how the characteristics the raters attributed to EVT and AdSD present in the subject videos.

Data Analysis

The results of the three individual raters for each of the 34 subjects were put into a spreadsheet for statistical analysis. Further analysis was conducted using SAS 9.4 (SAS Institute Inc., Cary, NC). The GLIMMIX Procedure was used to determine any differentiation between the three diagnostic groups by the fifteen subjective parameters. Inter-rater reliability was determined using Cohen's kappa.

In order to establish intra-rater reliability for judgments on subjective visual perceptual parameters, the data set was reviewed a second time by each rater. Given the small sample size, the entirety of the data set was used to ensure for statistical relevance. Spearman's rank correlation coefficient (Spearman's rho) was used to examine intra-rater reliability.

CHAPTER 3. RESULTS

All three raters reviewed the thirty-four videos selected for evaluation across the fifteen subjective parameters. For the purposes of this exploratory study, the raters were split into two groups novice (n=2) and expert (n=1) given the level of stroboscopic experience to demonstrate a limited, but varied level of knowledge.

Inter-rater Reliability

Inter-rater reliability was calculated using Cohen's kappa coefficient. Taking the likelihood of chance agreement into consideration, Kappa determines the raters' precision based upon the magnitude of agreement between raters. Kappa is a measure of this difference, standardized on a 0 to 1 scale, where 1 is perfect agreement and 0 is what would be expected by chance. The statistical significance for Kappa was set by the alpha ($p < .05$). Here, the statistical significance represents the minimum requirement to disregard agreement purely by chance. To determine whether any parameters which met this minimum significance also demonstrated substantive magnitude, the scale first proposed by Landis and Koch (1979) was used (Table 3.1).

Table 3.1
Interpretation of Kappa

Kappa	Strength of Agreement
0	poor
.01-.20	slight
.21-.40	fair
.41-.60	moderate
.61-.80	substantial
.81-1.0	almost perfect

Overall, nine of the fifteen parameters met the minimum significance set by the alpha. Two parameters, the arytenoid tremor location and right/left true vocal fold symmetry demonstrated only a "slight" measure of agreement. Six of the parameters fell within the boundaries of "fair" agreement (Table 3.2). One parameter, complete cessation of TVF vibration met “moderate” criteria. Following Landis and Koch’s interpretations, no parameters met their criteria for “substantial” agreement (.61-.80). Seven of the fifteen parameters demonstrated insignificant interrater agreement, see Table 3.2.

Table 3.2.
Inter-rater Reliability of Subjective Endoscopic Parameters based upon Cohen’s kappa

Endoscopic Parameter	Kappa	Group Inter-rater Reliability (n=3)	Strength of Agreement
Pharyngeal Tremor	0.036337	0.35681 ɫ	--
Arytenoid Tremor	0.27023	0.003174936*	fair
Arytenoid Tremor Location	0.16220	0.004786018*	slight
Complete Cessation of TVF Vibration	0.51754	8.6187E-8 ɫ	moderate
Presence of Rhythmic Supraglottic Oscillation	0.34194	0.000276805*	fair
Location of Rhythmic Supraglottic Oscillation	0.29461	0.000015443*	fair
Supraglottic Activity During Voice Initiation/Glottal Attack	0.34945	0.000000479*	fair
Arytenoid Twitch	0.11841	0.11587 ɫ	--
Supraglottic Activity During Sustained Phonation/Constant	0.24213	0.000056855*	fair
Severity of FVF Involvement	0.10488	0.093550 ɫ	--
Intermittent FVF Adduction/Involvement	0.055575	0.24160 ɫ	--
Regularity of Vibration	0.066106	0.17330 ɫ	--
Right/Left TVF Symmetry	0.17647	0.037353*	slight
Anterior/Posterior TVF Symmetry Of the Same Fold	0.27900	0.002417825*	fair
Phase Symmetry	0.12888	0.096519 ɫ	--

* Statistical reliability with p< 0.05
ɫ Selected parameters did not have adequate statistical reliability
Landis and Koch propose the following as standards for strength of agreement for the kappa coefficient: ≤0=poor, .01– .20=slight, .21–.40=fair, .41–.60=moderate, .61–.80=substantial, and .81–1=almost perfect

Intra-rater Reliability

Intra-rater reliability of the raters for each of the parameters was calculated using Spearman’s rank correlation coefficient (Spearman’s rho). This measured the strength of the association between the two sets of ratings for each rater. Spearman’s rho is standardized on a -1 to 1 scale, where 1 is a direct correlation, -1 reflects an inverse correlation, and 0 being no correlation. The statistical significance for Spearman’s rho was set by the alpha ($p < .05$). Given

Spearman’s rho, the magnitude of the correlation was then interpreted based upon a scale for social science data with .2 being the recommended minimum effect size, .5 being of moderate effect, and .8 being of a strong effect to determine the strength of the correlation (Ferguson, 2009).

Results from the raters revealed mixed intra-rater reliability, with stronger agreement for supraglottic parameters over vocal fold vibratory parameters (Table 3.3).

Table 3.3.
Intra-rater Reliability of Subjective Endoscopic Parameters based upon Spearman’s rho

Endoscopic Parameter	Rater 1	Rater 2	Rater 3
Pharyngeal Tremor	1.00*	0.491	1.00*
Arytenoid Tremor	0.503	0.198	0.852*
Arytenoid Tremor Location	0.564	0.183	0.863*
Complete Cessation of TVF Vibration	0.821*	0.549	0.869*
Presence of Rhythmic Supraglottic Oscillation	0.817*	0.485	0.927*
Location of Rhythmic Supraglottic Oscillation	0.796	0.491	0.900*
Supraglottic Activity During Voice Initiation/Glottal Attack	0.849*	0.679	0.849*
Arytenoid Twitch	0.461	0.622	0.530
Supraglottic Activity During Sustained Phonation/Constant	0.811*	0.286	0.811*
Severity of FVF Involvement	0.898*	0.191	0.633
Intermittent FVF Adduction/Involvement	0.801*	0.566	0.878*
Regularity of Vibration	0.582	0.051	0.864*
Right/Left TVF Symmetry	0.571	0.299	0.482
Anterior/Posterior TVF Symmetry Of the Same Fold	0.555	0.383	0.335
Phase Symmetry	0.660	0.272	0.424
Mean across all parameters	0.713	0.383	0.75

Note: .2 = minimal effect; .5 = moderate effect; .8 = strong effect
*= strong effect

Two raters, Rater 1 and Rater 3 demonstrated relatively high consistency in their overall ratings reaching a mean of above 0.7. Rater 2 did not display similar consistency, with an overall agreement below a moderate effect of 0.5. Neither of the inexperienced raters (Rater 1 and Rater

2) reached a “strong” effect (0.8) for any of the vocal fold vibratory parameters. The experienced rater (Rater 3) reached a “strong” effect for their judgment of the Regularity of Vibration, but scored below a “moderate” (0.5) effect for the other vibratory parameters. Overall, the experienced rater demonstrated the highest level of agreement ($r = .75$) amongst the raters.

Differentiation of Subjective Endoscopic Parameters

Differentiation between diagnostic groups was determined using The GLIMMIX procedure; comparing each rater’s score for the fifteen parameters across each of the thirty-four subjects. This procedure is a generalized linear mixed model which allows for the analysis of multivariate data in which observations do not all have the same distribution, while also taking into account non-normative data and randomized effects (Schabenberger, 2014). The model is not a measure of correlation, but rather the probability of the three diagnostic categories being distinct across each parameter rather than distributed by chance or too similar to afford no true differentiation. The statistical significance was set by the alpha ($p<0.05$).

Overall, none of the hypothesized supraglottic parameters demonstrated significant distinction between diagnostic groups given the three raters’ responses. That is, each of these parameters was too evenly distributed between the three categories to offer any distinct patterns using high-speed endoscopy for these supraglottic features. See Table 3.4 for greater detail.

The specified vocal fold vibratory parameters, however, did reveal adequate statistical distinction between diagnostic groups (Table 3.4). While all four vocal fold vibratory parameters revealed distinctive patterns between the three diagnostic categories, only two, right/left TVF symmetry and anterior/posterior TVF symmetry, met the requirements for both reliability and differentiation (Table 3.5).

Table 3.4 Differentiation of Subjective Endoscopic Parameters Based Upon The GLIMMIX Procedure			
Endoscopic Parameter	Group Inter-rater Reliability (n=3)	F Value	p> 0.05
Pharyngeal Tremor	0.35681 ɫ	2.36	0.1115≠
Arytenoid Tremor	0.003174936*	0.05	0.9502≠
Arytenoid Tremor Location	0.004786018*	0.12	0.8889≠
Complete Cessation of TVF Vibration	8.6187E-8 ɫ	0.09	0.9180≠
Presence of Rhythmic Supraglottic Oscillation	0.000276805*	0.95	0.3960≠
Location of Rhythmic Supraglottic Oscillation	0.000015443*	0.95	0.3960≠
Supraglottic Activity During Voice Initiation/Glottal Attack	0.000000479*	0.31	0.7346≠
Arytenoid Twitch	0.11587 ɫ	0.78	0.4688≠
Supraglottic Activity During Sustained Phonation/Constant	0.000056855*	2.50	0.0988≠
Severity of FVF Involvement	0.093550 ɫ	1.79	0.1830≠
Intermittent FVF Adduction/Involvement	0.24160 ɫ	0.59	0.5591≠
Regularity of Vibration	0.17330 ɫ	4.40	0.0208+
Right/Left TVF Symmetry	0.037353*	4.02	0.0280+
Anterior/Posterior TVF Symmetry Of the Same Fold	0.002417825*	3.44	0.0447+
Phase Symmetry	0.096519 ɫ	4.30	0.0225+
* Statistical reliability with p> 0.05 ɫ Selected parameters did not have adequate statistical reliability + Statistical distinction shown between diagnostic groups with p>0.05 ≠ Selected parameters did not have adequate statistical distinction between identified diagnostic groups			

Table 3.5 Differentiation of TVF Parameters			
Endoscopic Parameter	Essential Voice Tremor	Adductor Spasmodic Dysphonia	Both
Regularity of Vibration ɫ	62.50%	85.42%	56.67%
Right/Left TVF Symmetry*	50.00%	35.42%	73.33%
Anterior/Posterior TVF Symmetry Of the Same Fold*	41.67%	20.00%	56.67%
Phase Symmetry ɫ	58.33%	39.58%	76.67%
* Statistical reliability with p> 0.05 ɫ Selected parameters did not have adequate statistical reliability			

CHAPTER 4. DISCUSSION

This preliminary investigation sought to differentiate two voice disorders based upon supraglottal events and vocal fold vibratory characteristics selected from evidence within the existing literature. The reliability of the raters was also analyzed to determine the viability of the ratings and the level of expertise required to make informed judgments using high-speed videoendoscopy. Intra-rater reliability suggested a positive relationship between level of voice experience and more consistent judgments. Results demonstrated mixed inter-rater reliability for supraglottic and vocal fold vibratory parameters, with insignificant reliability for parameters which asked raters to clarify the degree of severity. Only two of the fifteen parameters provided adequate reliability and differentiation, right/left vocal fold symmetry and anterior/posterior vocal fold symmetry. None of the hypothesized supraglottic parameters demonstrated any significant distinction between diagnostic groups given the three raters' responses. While all four vocal fold vibratory parameters revealed distinctive patterns between the three diagnostic categories, only two, right/left TVF symmetry and anterior/posterior TVF symmetry, met the requirements for both reliability and differentiation. For these two parameters, EVT demonstrated greater vocal fold symmetry in comparison to AdSD; however, those with a differential diagnosis of both (AdSD with Vocal Tremor) demonstrated the highest vocal fold symmetry of the three diagnostic groups.

Differentiation for Groups Across Subjective Endoscopic Parameters

A detailed analysis and review of the subjective visual perceptual parameters for HSV identified few distinctive markers that could be applied towards differential diagnosis for clear separation. Contrary to the initial hypothesis, none of the supraglottal events proposed to identify AdSD or EVT reached significant variation for any of the parameters to diffentiate between the groups. The vocal fold vibratory characteristics, however, fared better, with all four parameters providing sufficient differentiation (Table 3.4). It should be noted, however, that while these four parameters differentiated between the disorders, not all met statistical significance for inter-rater reliability.

While it was hypothesized that vocal fold vibratory characteristics would provide greater distinction between EVT and AdSD compared to supraglottic characteristics, it was surprising for the supraglottal events to demonstrate such muddled results given the separate perceptual characteristics attributed in the literature (Ludlow, 2012; Sulica & Louis, 2010; Patel, et al., 2011; Colton, et al., 2011; Tanner et al., 2012; Warrick et al., 2000; Lester et al., 2013). This discrepancy may be due to several factors. First, while the faster playback rate of 200 fps mimicked a stroboscopy rate, videos taken in high-speed versus those taken via stroboscopy are not mirror replicas. Raters reported certain parameters, such as arytenoid twitch, difficult to identify given the intermittent movement of the arytenoids and the slower playback rate. This may have biased raters in their judgments for such parameters, over or underestimating the presence of a particular characteristic. Second, a consistent view of the posterior pharyngeal wall was not present for all videos, often cropped out of the shot with a focus on the vocal folds. Since a defining diagnostic characteristic such as pharyngeal tremor was excluded with the HSV, this may also contribute to the lack of differentiation between the two disorders.

The documented overlap between the disorders may also contribute to the lack of separation for most parameters. Results from this study suggest that supraglottic events examined via HSV alone may not offer a distinction. All identifiers including age, gender, case history, and audio perceptual information were stripped from the subjects, leaving the raters blind. This was done to isolate the visual perceptual parameters, but in the clinical setting all information is weighed to make an informed diagnosis and plan for treatment. Future studies are warranted if inclusion of acoustic, stroboscopy, perceptual, and background voice history will improve the differential diagnosis rate between these disorders.

Although all selected vocal fold vibratory parameters produced sufficient statistical separation between the disorders, only two of the four were also reliable amongst the raters (Table 3.4). Analyzing these two parameters further, AdSD showed greater irregularity for right/left and anterior/posterior TVF symmetry compared to EVT as hypothesized. Only 40-50% of the cases for EVT demonstrated symmetry along the same fold and between folds (Table 3.5). Although the differentiation reached a level of statistical significance that cannot be attributed to chance distribution, the question of whether the level of magnitude of the difference is high enough to influence a clinical diagnosis remains uncertain. Development of objective HSV vibratory assessment protocol might address the reliability issues and help with better differential diagnosis.

It is of interest to note, however, that instances wherein a subject had a diagnosis of AdSD with Vocal Tremor, the symmetry for both of these parameters was higher than that of those with Essential Voice Tremor alone (Table 3.5). Given combined components and the presence of intermittent spasm/adductory motion of vocal folds for AdSD with Tremor, the higher degree of symmetry is of interest. This finding illuminates the complex presentation of these two disorders, made all the more difficult with the overlap between.

Patel et al. (2011) examined the vibratory features of the vocal folds using HSV and determined motion irregularities and micro-motions of the true vocal folds to be novel characteristics for AdSD against muscle tension dysphonia. Although EVT, AdSD, and MTD have shown similar audio perceptual presentations, given the rather even distribution of the parameters across EVT and AdSD in this study, AdSD and EVT may present with less distinctive visual perceptual characteristics in comparison to AdSD and MTD. This may also stem, in part, from the difference in etiology; with EVT and AdSD being involuntary neuromuscular conditions whereas MTD can fall within voluntary control with appropriate voice therapy.

Reliability

When ascertaining the degree of reliability both between and within raters, it is important to distinguish between accuracy and precision. The findings for this exploratory study focused solely on precision. If results are very precise, diagnostic guides can be created to increase accuracy. For this task, raters were not asked to determine a diagnosis of EVT, AdSD or Both. Ideally, parameters that convey distinctive and reliable properties using HSV may be identified, and serve as an additional tool in forming a differential diagnosis in the clinical setting.

Inter-rater reliability

Overall, raters significantly agreed on the presence or absence of most major subjective visual perceptual parameters hypothesized as defining characteristics of EVT or AdSD in this study. While the findings of the study call into question the novelty of these characteristics between EVT and AdSD, the raters regardless of level of experience were able to agree in their selection of pertinent parameters. This suggests that HSV, as supported by the literature, is a viable tool in the examination of supraglottic events along with vocal fold vibratory movement.

Several parameters, including: intermittent false vocal fold adduction, the degree of false vocal fold severity, and the regularity of vocal fold vibration, offered statistically insignificant results, within the degree of chance. One source of error may be attributed to individual rater bias based upon their determination of the degree of variation or severity. Non-binary parameters based on the location of a given observation did not demonstrate similar differences. The intermittent false vocal fold adduction was an added parameter based upon initial observations of the videos which may have suffered from a lack of sufficient clarity in its definition amongst the raters.

It was originally hypothesized that vocal fold vibratory parameters would demonstrate greater inter-rater reliability compared to supraglottic characteristics. The findings offer mixed results, with 6 out of 11 supraglottic events meeting the minimum significance to rule out chance compared with 2 out of 4 of the vocal fold vibratory characteristics. Symmetry of the true vocal folds both along the same length and opposite demonstrated significant reliability. These findings follow the high reliability of vocal fold symmetry reported from Rosen (2005) and confirm its use in analyzing high-speed vocal fold vibratory patterns.

Mirroring the results of supraglottic parameters, the vocal fold vibratory parameter which required the rater to use a scale of severity demonstrated less reliability amongst the raters when compared to the parameters which required a judgment of presence or absence alone. As such, regularity of vibration for the vocal folds may by its nature prove to be a parameter more susceptible to an individual rater's bias based upon their experience and reference point for regularity. Although phase symmetry has been established for HSV analysis (Patel et al., 2008; Yamauchi et al., 2012), the minimal significant reliability was not reached for this study. Patel et al. (2008), in a study comparing stroboscopy and HSV found phase symmetry to have high intra-rater and inter-rater reliability between a range of normal and disordered voices including AdSD. That study, however, did not include individuals with EVT. In a later study, Patel et al. (2011), found higher inter-rater reliability in their study comparing Muscle Tension Dysphonia to AdSD.

This parameter may be harder to distinguish with moderate to severe aperiodic voices such as EVT and AdSD which share such similar characteristics and etiologies in comparison to other voice disorders. The overlap of the two disorders may also decrease inter-rater reliability, especially given that diagnosed as Both (AdSD with Tremor) presented with greater symmetry than either disorder alone.

Out of all the parameters, complete cessation of the vocal folds demonstrated the highest magnitude of agreement between the raters. This is to be expected based upon how HSV allows the rater the detail required to discern the pattern of the vocal fold vibration. The definition of this parameter is also succinct in its dimensions with less room for subjective bias. Yet this "moderate" level of magnitude (.41-.60) as defined by Landis and Koch does not reach the level suggested for substantial agreement between raters (.61-.80). It is not enough to establish the reliability at the minimum point above chance. The strength of the agreement ought to also be considered when weighing the impact of a particular parameter. The other parameters which met significant agreement fell between slight (.01-.20) and fair (.21-.40) levels of magnitude.

Other studies have found mixed results for the level of inter-rater agreement using stroboscopy Rosen (2005) identified a single vocal fold vibratory parameter in their investigation of stroboscopy that met the "substantial" criteria. Amplitude, symmetry, duration, and closure pattern all were reported to fall within between fair (.21-.40) and moderate (.41-.60) agreement (Rosen 2005). In an analysis of the diagnostic capabilities of strobe and HSV, Mendelsohn et al. (2013) found similar levels of magnitude for stroboscopy and HSV when laryngologists determined differential diagnosis for vocal lesions and other voice disorders. Polyps proved to be the single disorder with substantial agreement (.61-.80) between raters via stroboscopy, with the rest falling between fair and moderate agreement for both stroboscopy and HSV (Mendelsohn et al., 2013). Patel et al. (2008) reported a high inter-rater reliability between 70-78% via Pearson's coefficient with their analysis of similar HSV vibratory features including amplitude, symmetry, closure pattern, and periodicity, and mucosal wave. However, they did not differentiate the reliability for each parameter.

This investigation's and others' findings suggest a need for greater strength in the reliability for subjective endoscopic parameters. Greater training and specific reference points along with using raters with more experience may increase inter-rater reliability. However, length and depth of experience alone may not be enough. In a side analysis using this study's same subjects, two laryngologists, including the same laryngologist who made the initial diagnosis, rated the same subject videos for diagnosis. They determined 61% exact agreement between EVT, AdSD, or Both. Although they only outright differed on 6% of the cases, 33% of the time one identified a sole diagnosis while the other saw an overlap of both. This mirrors the initial results reported by the Dystonia coalition which found 50% agreement on endoscopic evaluations for EVT and AdSD (Ludlow, 2012). This variation in diagnosis may reflect the lack of distinction found in this study between supraglottic visual perceptual parameters. It also calls into question the accuracy of the diagnosis and the difficulty of determining distinctive parameters given the potential variability for challenging cases.

Intra-rater reliability

Overall across the ratings, as hypothesized, the rater with the most experience with stroboscopy (Rater 3) demonstrated the highest level of consistency between the two sets of ratings for the videos. The two inexperienced raters displayed greater variability in their judgment of the parameters. Rater 1 demonstrated more consistency in their ratings compared to Rater 2 (Table 3.3). Experience alone, however, may not be the sole determinant of precision for videoendoscopy. Rosen (2005) reported the rater with the highest intra-rater reliability (0.99) to be a "novice" for voice experience; however it is worth noting that all of their raters labeled "expert" fell between 0.77-0.93, whereas most "novice" raters fell below 0.75 for intra-rater reliability. For this study, both Rater 1 (inexperienced) and Rater 3 (experienced) scored above a "strong" effect (> 0.80) on most supra-glottal parameters. Rater 2, however, proved to be an outlier, scoring below a "moderate" (0.50) level for their overall ratings. With the least stroboscopy experience, Rater 2 would have benefitted from a more intensive training session in order to reach a level of better reliability.

While the overall intra-rater reliability is important to consider, analyzing the raters' reliability at the level of each parameter can offer additional feedback for developing the best parameters for diagnostics. Given the results, certain parameters may require additional experience in order to detect them reliably via HSV. Rater 3 demonstrated "strong" agreement for arytenoid tremor, whereas inexperienced raters produced only "moderate" or below "minimal" agreement. Other parameters such as arytenoid twitch proved too intermittent for any rater to consistently observe.

Consistency for the vocal fold vibratory parameters specifically proved to be a greater challenge. Analyzing the magnitude of the correlation, Rater 3 demonstrated "strong" consistency in identifying the regularity of vibration, where the two inexperienced raters did not. However, none of the raters' demonstrated a "strong" level of agreement for the other three vocal fold vibratory parameters. This reflects a need for greater familiarity with laryngeal imaging and also for more extensive training methods with visual examples for each parameter.

In their analysis of intra-rater reliability, Rosen (2005) suggested implementing selection criteria for an intra-rater reliability of 0.80 or higher for raters in order to better control for potential outlying effects and improve the overall reliability of stroboscopy as a diagnostic tool. None of the raters for this study met such criteria given their mean results. However, several factors may have impacted the precision of the raters' judgments; particularly for the vocal fold vibratory parameters. Spearman's rho is a measure of correlation of a rater's precision, and therefore it does not take into account the level of accuracy of each judgment. Increased familiarity of the parameters themselves may have been reflected in a change of detection or degree of severity for the inexperienced raters. The structure of the numbering system of the rating form, with a change from supraglottic parameters to vocal fold vibratory parameters, may have increased confusion and also impacted raters' responses—decreasing the correlation for vocal fold parameters.

In a side analysis of this study's same subjects, the same laryngologist who determined the initial diagnosis was asked to view each case blind and once more attribute a diagnosis. The laryngologist demonstrated 44% exact agreement from his earlier diagnosis. The laryngologist changed his answer to or from both (AdSD with Vocal Tremor) 41% of the time and demonstrated 15% reversal for whether a subject video might be AdSD or EVT. As with the inter-rater reliability, much of the difference circles around the overlap of these two disorders and how such a combination may present.

Clinical Implications

The most important take away from this exploratory study is that while HSV is a viable tool that can be used to examine aperiodic voices, it ought to be employed in conjunction with other methods as reflected in clinical practice. HSV video devoid of acoustic measures, the patient's physical presentation, and medical case history may not be suitable for distinguishing between EVT and AdSD. While the findings supported the use of HSV based upon the raters' overall reliability, the individual parameters did not separate the two disorders as hypothesized. Instead, all but two of the parameters presented with similar distributions across all three groups. However, given the potential variability in the diagnosis itself, it remains a pertinent question of how one may draw parameters that accurately reflect the disorder. Based upon the results, examining the degree of vocal fold symmetry may be a contributing feature worth taking into consideration in establishing a differential diagnosis when pairing HSV with a balanced clinical evaluation.

Limitations

There are several factors which pose limitations with the interpretation of the data. Results based upon a small sample size for the voice disorders may not reflect a larger sample pool. Given the variability of individuals seen in a clinical setting, the balance of the three groups was not evenly distributed, which may skew the outcomes. The number of raters, with only one experienced rater, also constricted any effects which may be extrapolated based upon the level of experience and familiarity with laryngeal imaging. In order to establish proper reliability and accuracy, it is important to understand the point at which an individual may be both consistent and valid in their ratings. A larger and more diverse group of raters is required in order to establish the limited evidence provided by this study that the degree of familiarity with stroboscopy may influence the reliability of raters' scores.

The level of instruction for the parameters may have influenced the raters' judgment for each subject. Clearer descriptions and definitions of the targeted parameters, with accompanying video and specific training would also likely improve reliability. This could be improved through the use of anchors, as suggested by Rosen (2005) wherein the raters are provided an external, common reference for each subjective visual perceptual parameter upon. Fatigue for the individual raters across the rating of all video subjects may also be a potential limitation when completed together in one to two sittings.

Implications for Future Research

The findings from this initial investigation provide preliminary data for the future exploration of HSV for differentiating parameters towards diagnosis for EVT and AdSD. Additional probes are required in order to distinguish the determinants of the parameters' reliability. Future research should seek to increase the number of subjects included for a greater range of diagnostic cases and expand the number of raters to ascertain the level of experience required to discern qualities for these particular voice disorders. The level of severity for the two vocal fold disorders may impact differentiation as well. In particular, vocal fold vibratory symmetry should be further examined as a distinctive feature for EVT versus AdSD. The complicated involvement of AdSD with Tremor in regards to such differentiation should also be further examined. Whether the higher level of symmetry is a distinctive feature or whether it is due to a lack of reliability for diagnosis between the two disorders remains uncertain.

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APPENDIX A

Description of Visual Subjective Endoscopic Parameters

Essential Voice Tremor Features

- Pharyngeal Tremor (palate, tongue, posterior pharyngeal wall, lateral pharyngeal wall)
  Rhythmic movement of the noted structures.

- Arytenoid Tremor
  Rhythmic movement of the arytenoid cartilages

- Arytenoid Tremor Location (L, R, Both)

- Complete Cessation of TVF vibration
  The TVFs stop their vibratory movement during phonation.

- Presence of Rhythmic Supraglottic Activity/Oscillation
  Rhythmic anterior/posterior or lateral compression inward of the supraglottic structures during phonation

- Location of Rhythmic Oscillation (None, A/P, Lateral, or both)

Adductor Spasmodic Dysphonia Features

- Supraglottic activity during voice initiation/glottal attack
  Compression of FVF and supraglottic structures during the onset of vibratory motion following respiration

- Arytenoid Twitch
  Intermittent movement of the arytenoid cartilages

- Supraglottic Activity during Sustained Phonation – Constant
  Consistent presence of supraglottic involvement during phonation, specifically with the FVF

- Severity of FVF Involvement (Absent, Partial, Complete)

Other

- Intermittent FVF adduction
  The FVFs demonstrate intermittent involvement that is neither constant nor rhythmical in nature. The FVFs adduct and come together towards midline before returning back to their previous position.

Vibratory Features

- Regularity of Vibration
  TVFs come together with regular precision and consistent duration of glottal cycles.

- R/L Symmetry
  Both L and R TVF come together with the same pattern, in sync.

- A/P Symmetry
  Both the anterior and posterior portion of each TVF come together with the same pattern top and bottom, in sync together.

- Phase Symmetry
  The TVFs come together and meet at midline.

APPENDIX B

Subjective Rating Form for High-Speed Videoendoscopic Evaluation: Voice Initiation Period and Sustained Phonation Features in Essential Voice Tremor and Adductor Spasmodic Dysphonia

			Tremor Features*						**AdSD Features***		**Other**		**Vibratory Features***		
Subject #	**Phx Tremor**	**Arytenoid Tremor**	**Arytenoid Tremor Location**	**Complete cessation of VF vibration**	**Presence of RHYTHMIC supraglottic oscillation**	**Presence of RHYTHMIC supraglottic oscillation/ LOCATION**	**Supra glottic activity during VOICE INITITATION Glottal attack**	**Arytenoid twitch**	**Supra glottic activity during sustained phonation /CONSTANT**	**Severity of FVF involvement**	**Intermittent FVF Adduction/ Involvement**	**Regularity of vibration**	**R/L TVF symmetry**	**A-P symmetry on the same fold**	**Phase symmetry**
	Palate Tongue PPW LPW	1=not present 2=present	**R:1 L:2 Both:3**	1=not present 2=present	1=not present 2=present	**None: 0 Lateral: 1 A-P: 2 Both: 3**	FVF involvement 1=absent 2=partial 3=complete	1=not present 2=present	**None: 0 Lateral: 1 A-P: 2 Both: 3**	1=absent 2=partial 3=complete	1=absent 2=partial 3=complete	1=regular 2=somewhat regular **3: irregular**	**1=not present** 2=present	**1=not present** 2=present	**1=not present** 2=present
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*Note: the labeling of the hypothesized differentiation amongst the parameters was not included on the actual rating form

VITA

Lindsey A. Parker was raised in Berea, Ohio, a suburb of Cleveland. She graduated cum laude with a Bachelor of Arts in English Literature from Northwestern University in 2010. Since then, she has completed four novel manuscripts, and discovered speech-language pathology. She began her studies at Louisiana State University in 2012.

From the first slides in anatomy and physiology, the larynx stole Lindsey's attention. She thought the endoscopic view of the vocal folds shared a passing resemblance to a peculiar cuttlefish eye, and she has not been able to tear her gaze away since. This thesis is an extension of that fascination. Upon completion of her master's degree in May 2015, she plans to complete her clinical fellowship specializing in voice and swallowing disorders and to work towards publishing a novel.