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**Associations between laryngeal and cough dysfunction in motor
neuron disease with bulbar involvement**

by
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A dissertation
Submitted in partial fulfillment of the
Requirements for the degree of
DOCTOR OF PHILOSOPHY in REHABILITATION SCIENCE

University of Washington
2012

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Program Authorized to Offer Degree:
Rehabilitation Sciences

ABSTRACT

PURPOSE: Cough, a fundamental mechanism in airway protection, depends on true vocal fold (TVF) function and airflow. In individuals with motor neuron disease (MND), cough impairment leads to increased risk for aspiration and respiratory failure. This study characterizes differences and associations between TVF kinematics and airflow during cough in individuals with bulbar MND.

METHODS: Sequential glottal angles associated with TVF adduction and abduction across the phases of volitional cough were analyzed from laryngeal videoendoscopy exams of adults with bulbar MND (n=12) and healthy age-matched controls (n=12) and compared with simultaneously collected cough-related airflow measures.

RESULTS: Significant differences between MND and control subjects were observed with the following airflow and TVF measures: peak expiratory cough flow (PECF) ($p=0.01$), expiratory phase rise time (EPRT) ($p=0.004$), volume acceleration ($p<0.001$), maximum TVF angle during expulsion phase post-compression abduction (approached significance $p=0.06$), and expulsion phase post-compression abduction TVF angle average velocity ($p=0.003$). All subjects demonstrated complete TVF and supraglottic closure during the compression phase of cough, except 2/12 MND subjects demonstrated incomplete supraglottic closure. Maximum post-compression TVF abduction angle and post-compression TVF abduction angular velocity were statistically correlated with PECF ($r = 0.49$; $p = 0.02$) and EPRT ($r = -0.66$; $p = 0.001$), respectively, when data were analyzed for MND and control participants combined. However this may represent artifact owing to the variable distributions in each group. Correlational analyses for the groups separately were not statistically significant, except the correlation between post-compression maximum TVF abduction angle and PECF demonstrated a strong positive relationship and approached significance in the MND group ($r = 0.57$; $p = 0.09$).

CONCLUSIONS: Reductions in the speed and extent of TVF abduction are seen during expulsion phase of cough in individuals with MND. This may contribute to cough impairment and morbidity.

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LIST OF ABBREVIATIONS

ALS	Amyotrophic lateral sclerosis
ALSFRS-R	ALS Functional Rating Scale-Revised
EPRT	Expiratory phase rise time
FVC	Forced vital capacity
L	Liters
L/s	Liters per second
LMN	Lower motor neuron
MEP	Maximum expiratory pressure
MIP	Maximum inspiratory pressure
MND	Motor neuron disease
PBP	Progressive bulbar palsy
PECF	Peak expiratory cough flow
PLS	Primary lateral sclerosis
PVT	Peak value time
s	Second
TVF	True vocal fold
UMN	Upper motor neuron
VA	Volume acceleration (PECF/EPRT)

ACKNOWLEDGEMENTS

First, I would like to acknowledge and express deep gratitude to all of the individuals who volunteered to participate with this research study, especially those living with motor neuron disease. These participants were willing to volunteer for this study in hopes that this information will lead to an improved understanding of the effect of motor neuron disease on the ability to cough, and so that this information could potentially benefit others facing a diagnosis of motor neuron disease. I plan to honor the participation of these volunteers by doing everything in my power to ensure that the study results are published and made available to the medical community to inform future research efforts related to motor neuron disease.

I am grateful for the funding that I have received from several sources throughout my graduate program: NIH/NIDCD F31 DC011689 (2011 – 2012); Walter C. and Anita C. Stolov Research Fund (2010-2011); NIH/NIDCD T32 Dept. Speech & Hearing Sciences (2008-2010); and RA Multiple Sclerosis Rehabilitation Research & Training Center (MSRRTC) (2006-2008).

I am grateful to my PhD Supervisory Committee members for their advice and guidance offered throughout the program and development of the dissertation research study. Kathryn Yorkston, PhD, has been an amazing advisor. She is solidly experienced, well known and respected in the Speech Pathology and Rehabilitation communities. I greatly appreciate her support in allowing me to pursue a novel dissertation topic, and supporting me through this process. Robert Miller, PhD, has offered me ongoing mentorship, guidance and support as well throughout my doctoral program. Dr. Miller's work in the area of dysphagia has inspired me to follow a similar path. From the time of working toward my Master's in Speech Pathology in the 1990s until now, I believe my pattern of critical thinking has been largely shaped by the work and teaching skills of Dr. Miller. I am grateful to Drs. Yorkston and Miller for providing me with multiple opportunities for gaining experience with publications and presentations. I appreciate Tanya Eadie, PhD, for providing access to resources at the Speech & Hearing Sciences Clinic, which were instrumental in completion of my pre-dissertation study, as well as for her advice pertaining to the dissertation study. Marcia Ciol, PhD, has been an invaluable resource for advice pertaining to study design and biostatistics. I greatly appreciate her advice and critical feedback. Finally, Beth Kerr, PhD, was of support to me, not only in her role as Graduate Student Representative on my committee, but also in offering advice pertaining to presentation of information in my NIH F31 grant submission.

This dissertation study has required multi-disciplinary collaboration. For this reason, this dissertation research would not have been possible without the support of two key medical collaborators: Joshua Benditt, MD (Professor in the Department of Pulmonary and Critical Care Medicine), and Albert Merati, MD (Professor in the Department of Otolaryngology, Head and Neck Surgery). Both took time from their busy schedules to meet with me, offer support and connect me with resources that were essential to complete this study. Another key collaborator/advisor on this study was Louie Boitano, MS, RRT. My idea for this was in part inspired by the work of Louie Boitano, who frequently observed the problem of potential true vocal fold obstruction of airflow when assessing individuals with motor neuron disease. His excellent publication "Management of airway clearance in neuromuscular disease" (Boitano, 2006) also served as an impetus for this study. In addition, I appreciate professionals in the departments of rehabilitation, neurology, otolaryngology and pulmonary medicine who helped with recruitment of participants for this research.

It truly did take a village of advisors to help me on the path of successful completion of this dissertation research study. Several others have also been supportive and instrumental in

helping me with my dissertation research. I would like to thank the following people: Cara E. Stepp, PhD, has been extraordinarily generous with her time, assistance, resources and advice concerning measurement and analysis of true vocal fold angle data. Dr. Stepp introduced me to James Kobler, PhD, at Harvard. Dr. Kobler generously allowed me to use the Matlab code he wrote for measurement of true vocal fold angles (previously published in Dailey et al. 2005). Carolyn Baylor, PhD, generously offered her time and expertise in assisting with reliability measures and discussing aspects of this study. Amanda Hu, MD, offered her time and assistance with performing the majority of the laryngeal endoscopy procedures associated with this study, as well as with assisting with recruitment of control participants and offering input regarding otolaryngology observations related to participant laryngeal endoscopy videos. Anders Lofqvist, PhD, from Haskins Laboratories, offered general advice regarding photoglottography. Ludo Max, PhD, generously assisted me with trialing use of photoglottography as a measurement tool, as well as with feedback and advice on data collections equipment and software. Robert Price, MSME, assisted with hard wiring, assembly and testing of the photosensor needed to trial use of photoglottography. Although not reported in this dissertation study, exploring use of photoglottography was an important part of developing methods for this study. Wayne Lamm, MA, and Mike Emery, PhD, from the UW and VA pulmonary research labs offered guidance and advice pertaining to spirometry equipment. I greatly appreciate the advice and guidance offered by Dr. Lynne Werner related to grant writing. Christine Sapienza, PhD, University of Florida, generously offered me advice and feedback related to my study and equipment for spirometry. Finally, I appreciate the guidance, strong support and leadership of Deborah Kartin, PhD, Director of the Rehabilitation Sciences PhD Program in the Department of Rehabilitation Medicine, University of Washington.

Last, but certainly not least, I would like to thank my immediate and extended family and my friends for their love and support. I would especially thank my husband, Tad, for being generous in his love, support and encouragement of my progress on this academic path that I have chosen. In addition, I would like to thank my mother (Catherine), brother (Roger), sister (Susan), as well as my nieces and nephew (Sasha, Rachel, Chrystal and Derrick) for sharing their love and encouragement! Finally, I would like to thank my mother- and father-in-law, Ramona and Walt, for their ongoing love and support.

DEDICATION

I would like to dedicate this research to all who have fought the battle with MND, especially those who volunteered for this study, James “Bud” Jones, as well as those who provide care to individuals with MND.

I would also like to dedicate this research to my nieces (Sasha, Rachel and Chrystal) and my nephew (Derrick). I hope that this work will inspire you to pursue your dreams.

CHAPTER I: INTRODUCTION

Statement of the problem

The ability to cough is an essential component of human pulmonary defenses.^{1,2} Adequacy of pulmonary defenses is an important consideration in the context of dysphagia assessment for rehabilitation patients. An effective cough defends the airway and lungs from aspiration, i.e., entry of food, liquid or saliva into the lower airway and lungs. “Dystussia” is a term that indicates an inability to cough effectively, in contrast to other medically abnormal conditions characterized by chronic cough, e.g., bronchitis. Dystussia is related to risk for aspiration and respiratory failure in people with neuromuscular dysfunction.³⁻⁸ It is well known that dystussia can occur due to weakness of the inspiratory and/or expiratory respiratory muscles.² In particular, weakness of the abdominal muscles results in difficulty generating sufficient pressure for a forceful, effective cough.² However, dystussia also occurs in people with conditions affecting the muscles for speech and swallowing, i.e., the bulbar musculature, even with normally functioning inspiratory and expiratory respiratory musculature.^{2,9}

Respiratory impairments and cough dysfunction are common in motor neuron diseases (MND) such as amyotrophic lateral sclerosis (ALS) and primary lateral sclerosis (PLS). ALS is a classic, major subtype of MND. Approximately 20% of people with ALS experience initial onset of weakness in the bulbar musculature.¹⁰ Most with ALS will experience bulbar involvement at some point in the course of the disease.¹⁰ The mechanism of cough dysfunction in people with ALS differs between those with primarily limb versus primarily bulbar involvement. Cough dysfunction in limb ALS occurs mainly due to weakness of expiratory musculature;¹¹ inspiratory muscle weakness can also contribute to this effect.^{12,13} However, even with little or no involvement of respiratory musculature, people with bulbar ALS can experience reductions in cough effectiveness.^{14,15} Cough effectiveness in this group is most likely affected by weakened

true vocal folds (TVFs) which results in reduced coordination of muscular responses with airflow and an inability to build adequate subglottal pressure and maintain upper airway patency during cough attempts.⁹ Although cough dysfunction in those with bulbar involvement is not well understood, it is recognized that people with bulbar ALS frequently experience laryngeal dysfunction.^{16,17} Examining TVF kinematics and adequacy of airway patency during cough has important clinician implications. For instance, cough dysfunction, especially when combined with bulbar impairments, leads to higher risk for respiratory failure. In addition, respiratory and cough-related intervention for individuals with MND who have significant bulbar involvement is challenging. Interventions such as non-invasive positive pressure ventilation and mechanical cough assistance prolong survival in individuals with limb-onset ALS and those with mild bulbar involvement, but it is not effective for those with moderate to severe bulbar involvement.^{9,18-20} To date, however, no studies have directly examined the relationship between TVF movements and cough dysfunction in bulbar ALS.

Literature review

Motor neuron disease (MND)

MND refers to a group of disorders that result in destruction of motor neurons, i.e., upper motor neurons (UMN) and lower motor neurons (LMN). Four types of adult onset MND are commonly recognized: 1) ALS; 2) progressive bulbar palsy (PBP); 3) PLS and 4) progressive muscle atrophy. Populations of interest in this study include the first three. See a summary of these three types of MND in Table 1.

Table 1. Types of motor adult onset neuron disease (MND) targeted in this study

<i>Type</i>	Classic Amyotrophic Lateral Sclerosis (ALS)	Progressive Bulbar Palsy (PBP)	Primary Lateral Sclerosis (PLS)
<i>Muscle involvement</i>	Bulbar & Spinal	Bulbar only	Bulbar & Spinal
<i>Motor neuron neurological signs</i>	UMN & LMN	UMN &/or LMN	UMN only <ul style="list-style-type: none"> • May or may not progress to diagnosis of ALS • If only UMN signs for ≥ 4 years, likely to be pure PLS²¹
<i>Prognosis</i>	Median survival 4.3 years ²²	Median Survival 2-3 years ²³ ; typically progresses to ALS	Survival much longer than ALS. Higher levels of independence for years or decades ²¹

UMN = upper motor neuron; LMN = lower motor neuron

Modified from: Miller & Britton²⁴

ALS, also known as Lou Gehrig's disease in the United States, is the most common of the four types of MND. ALS is characterized by an initially focal degeneration of upper and/or lower motor neurons leading to weakness of voluntary and involuntary muscles that subsequently spreads to other regions of the body. Degeneration associated with ALS occurs in the pyramidal neurons (Betz cells, 5th layer of cerebral cortex) of the precentral gyrus (area 4, motor cortex) and alpha motor neurons from the brainstem and spinal cord.²⁵ The precise etiology or pathophysiologic mechanism is unknown. For approximately 2/3 of individuals with ALS, degeneration will begin in the limbs (either upper and/or lower extremities). Approximately 1/3 of individuals with ALS will experience bulbar onset, i.e., PBP, resulting in dysarthria and dysphagia. Rarely, degeneration associated with ALS will begin in the muscles for respiration.²⁶ Respiratory failure is the leading cause of death for individuals with ALS.

PBP is essentially bulbar onset ALS.^{27,28} For those who survive the initial bulbar symptoms, PBP will virtually always progress on to classic ALS. Initial symptoms associated with PBP can involve LMNs, UMNs or a combination of UMNs & LMNs.

PLS is a less common form of MND. Unlike ALS, PLS involves degeneration of UMNs only. PLS may ultimately progress to classic ALS. However, some have a clinically “pure” PLS, i.e., UMN degeneration without LMN involvement for a period of at least four years.²¹ Similar to ALS, initial focal degeneration in PLS occurs in the limbs for most, but can also begin in the bulbar musculature.²⁹ Owing to the UMN involvement, muscle spasticity and slowness is common in this group. Survival for individuals with PLS tends to be much longer than those with ALS.

Respiratory impairments are inevitable for most individuals diagnosed with ALS and other forms of MND, contributing significantly to risk for aspiration and pulmonary complications and ultimately leading to death.^{20,30} This is true whether the patient has bulbar and/or limb involvement. Despite having no direct effect on the lungs, respiratory impairments associated with MND can occur in any aspect of the mechanical respiratory system, including respiratory centers located in the medulla and weakness of the respiratory musculature for inspiration and forced expiration³¹, and/or dysfunction of the bulbar muscles that help to maintain upper airway patency. Incoordination of swallowing with breathing may also occur.^{9,32} When significant bulbar paresis is combined with severe weakness of the inspiratory and expiratory respiratory muscles, a “lethal combination”,¹² respiratory failure is more likely to occur and invasive ventilation then becomes the only option for continued survival.¹² See Figure 1 below.

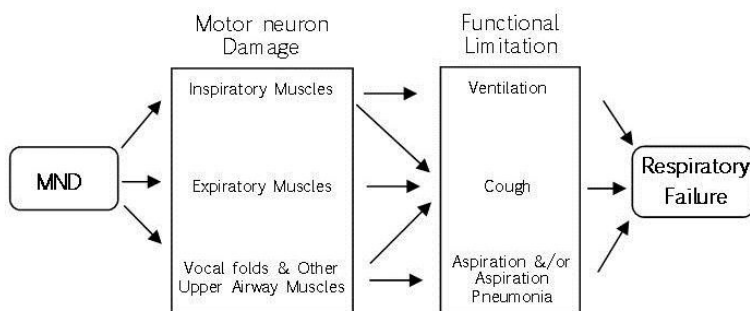


Figure 1. Functional effects of MND on the respiratory system
 Figure is modified from Benditt¹² and Yorkston and colleagues³³

Normal cough physiology

Cough is a key component of human pulmonary defenses that serves to protect the airway and lungs from aspiration of food, liquid, mucous, or other types of secretions. Specifically, cough is a type of respiratory maneuver in which the expired air (gas) couples with secretions of the lower airway and larynx in order to move tissues, secretions or other foreign materials (e.g., food) out of the lower airway and/or throat.³⁴ A protective cough response may be initiated volitionally or reflexively when sensory receptors within the mucosa of the larynx and lower airway regions are stimulated.² Effective coughing requires an intact cough reflex mechanism, as well as adequate respiratory and laryngeal muscle strength and coordination in order to generate high airflow velocity through the upper airway.^{34,35} Generation of high linear airflow velocity during cough is important for removal of secretions. Normally functioning adults can produce airflows as high as 11 L/s.^{36,37} Velocities commonly encountered in cough are frequently more than 2500 cm/second.³⁷

Airflow during normal cough: There are at least three sequential phases that facilitate the ability to cough normally: 1) inspiration; 2) compression (breath hold and intrathoracic pressure build); and 3) expulsion (forceful air expiration).² These phases of cough are depicted in Figures 2 and 3, below.

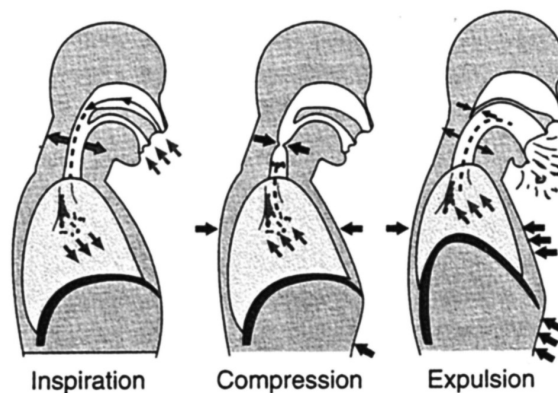


Figure 2. The phases of cough
Figure is modified from Fink & Hunt³⁸

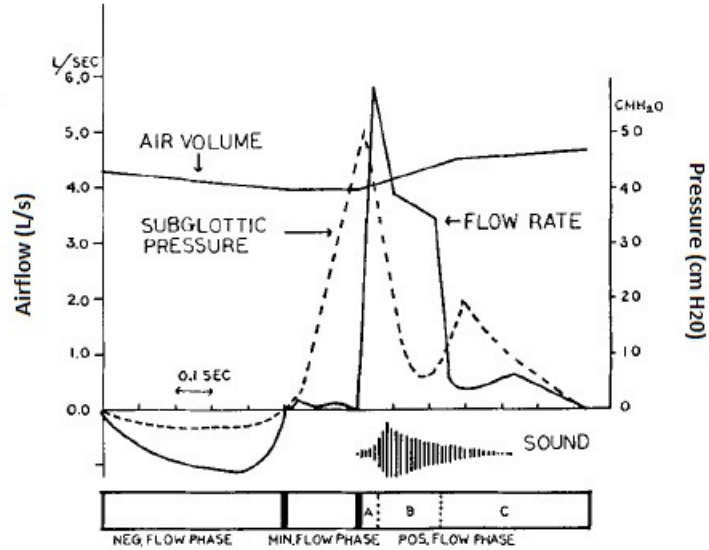


Figure 3. Schematic diagram of airflow and subglottic pressure across the phases of cough

Figure is from Yanagihara and colleagues³⁹

During the inspiration phase of cough, contraction of the diaphragm facilitates negative pressure build in the lungs, which serves to draw air in. The TVFs abduct widely during inspiration. During the compression phase of cough, intra-thoracic pressure increases. This is aided by glottic and supraglottic closure.⁴⁰ However, it is possible for individuals to effectively cough without glottic closure as well.³⁷ For instance, Young and colleagues argued that coughing can still be effective when the larynx has been completely bypassed, e.g., in people with tracheostomy and/or laryngectomy.⁴¹

During the expulsion phase of cough, the TVFs abduct and abdominal muscles aid expulsion. Dynamic compression of the airways reduces the tracheal cross-sectional area, resulting in a five-fold increase in the expiratory linear flow velocities and a 25-fold increase in the kinetic energy of the airstream³⁷ It is this energy that helps to “scrub” mucous from adherence to the airways. When a cough is initiated at a relatively high lung volume, this

dynamic compression occurs at the level of mainstem bronchi and trachea; it then extends more to the periphery as lung volume decreases, thereby “scrubbing” a longer section of the airway.³⁷

Respiratory muscle function during normal cough: During cough, mechanical and muscular forces are needed to move air in and out. The muscles of the respiratory system can be divided into two groups: respiratory pump muscles and respiratory valve muscles. The respiratory pump muscles include separate muscle groups that aid inspiration versus expiration. The diaphragm is the primary muscle of inspiration during the inspiratory phase of cough. The diaphragm moves downward with contraction, expanding the lungs and thoracic cavity. The external intercostals and accessory muscles further expand the thoracic cage. Expansion of thoracic space creates a negative air pressure within the lungs. Then, in accordance with Boyle’s Law, air flows from the region of relatively high pressure (atmosphere) to the region of relatively low air pressure (expanded lungs). Expiration during tidal breathing occurs passively as the muscles of inspiration relax. However, in the context of cough, expiratory muscles aid forced exhalation. The abdominal muscles provide the primary strength for forceful exhalation. The respiratory valve muscles consist primarily of the intrinsic laryngeal muscles that control vocal fold movements. The vocal folds have important functions related to the regulation of airflow associated with breathing. For instance, they actively abduct (open) to allow airflow in and out. During activities requiring protection of the airway, e.g., swallowing or vomiting, the vocal folds and supraglottic structures close to protect the airway. Function of the vocal folds and supraglottic structures during cough is described in further detail below.

Laryngeal function during normal cough: It is well known that respiratory muscles are needed for inspiration (e.g., the diaphragm), as well as for the pressure build up for forced expiration (e.g., abdominal muscles).² However, TVF movements are also a key component of cough physiology. A few studies of normal individuals have reported patterns of TVF movements based on electromyography (EMG) data and direct visualization of the TVFs during

cough.⁴²⁻⁴⁴ Although limited by small numbers of participants, these studies have provided valuable information on TVF function associated with cough. Synchronized, active TVF movements occur across all phases of cough. During inspiration, the TVFs abduct (open) to allow airflow to the lungs. Then, both the TVFs and supraglottic structures close with contraction of the abdominal muscles to aid build up of intrathoracic air pressure. In a 2001 EMG study of the laryngeal muscles during cough, Hillel discovered that the primary laryngeal abductor and tensor muscles, i.e, posterior cricoarytenoid and cricothyroid, begin to activate simultaneously with the adductors just prior to TVF abduction during expulsion.⁴² This results in an extremely rapid, “spring-load”-like, active abduction of the TVFs during the expulsion phase that occurs the instant that the laryngeal adductor muscles relax (see Figure 4). In an experiment with anaesthetized dogs, Sant’ Ambrogio and colleagues observed the same sort of intrinsic laryngeal muscle motor pattern, including active posterior cricoarytenoid and cricothyroid involvement during the expulsion phase of cough.⁴⁵ This pattern of muscle activation did not differ with the larynx isolated or connected to the lower airway, nor did it differ with intact versus sectioned internal branch of the superior laryngeal nerve. Thus, they concluded that the cough related pattern of intrinsic laryngeal muscle activation is centrally mediated and independent of laryngeal sensory feedback⁴⁵. Hillel has observed that the TVFs typically adduct again after expulsion.⁴² However, in 2012, Britton and colleagues observed variability of TVF closure after expulsion phase of cough, with approximately 50% of participants demonstrating TVF closure after expulsion.⁴⁰

In 1965, VonLeden & Isshiki reported that the false vocal folds (FVF) obscure the TVFs during the compression phase of the cough.⁴⁴ They also report that "except in a very gentle cough, the epiglottis covers the laryngeal inlet and obstructs view of the interior."⁴⁴ However, after systematically observing the pattern of TVF and supraglottic movements during the compression phase of cough during laryngeal endoscopy, Britton and colleagues reported

adequate visualization of the TVFs during expulsion phase of cough with use of modern laryngeal endoscopy equipment.⁴⁰ Britton and colleagues also systematically observed supraglottic function during the compression phase of cough. Across 95% of all coughs observed, a dynamic functional pattern of supraglottic reinforcement of airway closure was observed. Following closure of the TVFs, closure of supraglottic structures was achieved via extreme anterior-posterior compression, i.e., arytenoids contacted the petiole of the epiglottis, and approximation of the FVFs. These movements were further aided by squeezing of the pharyngeal walls, and created a supraglottic sphincter-like laryngeal closure. Upon expulsion, the supraglottic structures and TVFs popped open in concert within the time span of a single frame. In a very small number of samples (approx 5%), TVF closure was observed without this reinforcement of supraglottic structures; these were all very soft cough samples. These observations illustrate how supraglottic reinforcement aids the TVFs in achieving tight laryngeal closure during cough.

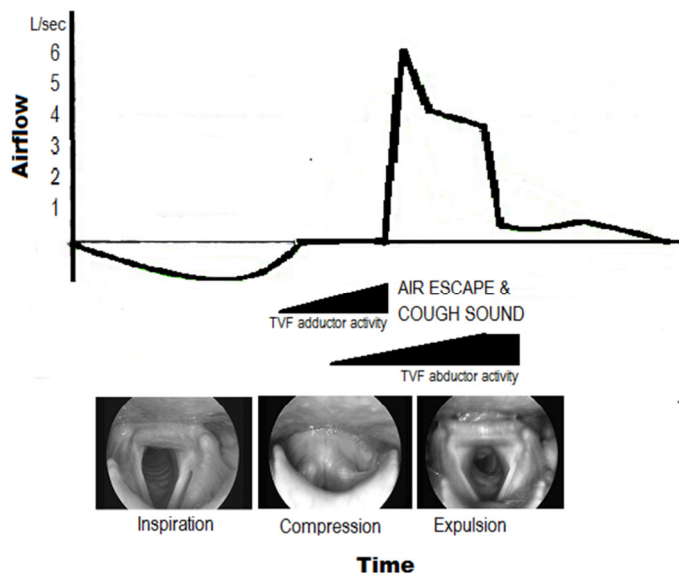


Figure 4. Schematic of TVF movements during a normal cough
 From Miller & Britton⁴⁶

Neurology of cough – spontaneous versus reflexive: Cough can be generated volitionally or spontaneously. Spontaneous cough is generated when afferent cough receptors in the airway are irritated. This irritation is conveyed through the vagus nerve on to the “cough center” in the brainstem, which then triggers the efferent cough response. Spontaneous cough is triggered via a complex reflex arc. The cough reflex arc includes afferent pathways (e.g., sensory nerve fibers from the vagus nerve that are located in the upper airways, a central “cough center” located in medulla of the brainstem⁴⁷ and an efferent pathway where motor impulses travel via vagus, phrenic and spinal nerves to the diaphragm, abdominal walls and laryngeal muscles. Cough receptors are located in the trachea, larger airways, pharynx and the larynx. Receptors in the laryngeal and tracheobronchial regions are sensitive to both mechanical and chemical stimuli.⁴⁸

A distinction between reflexively versus volitionally initiated cough is evident in the literature. Researchers have also distinguished reflexive cough from the "expiration reflex." A volitional cough is cortically mediated and can be initiated with or without laryngeal sensations or spoken requests.⁴⁹ Cough can also be suppressed volitionally. Conversely, a reflexive cough, i.e., "laryngeal cough reflex," is a brainstem mediated reflex triggered by sensations in the larynx, e.g., aspiration of food or liquid.⁴⁹ Finally, in contrast to the reflexive cough, the term "expiration reflex" refers to reflexive, forced expiration triggered by mechanical or chemical irritation of the vocal folds that occurs without a preceding inspiration.⁵⁰ Different patterns of motor activation of respiratory muscles have been observed in volitional versus reflexive cough.⁵¹ Muscular activation associated with volitional cough tends to occur more slowly than with reflexive cough, and it is characterized by a graded increase in the activation of expiratory respiratory muscles followed by activation of accessory muscles that is proportional to the cough flow rate. Conversely, reflexive cough is characterized by faster, stronger, and simultaneous activation of expiratory and accessory muscles. In contrast to volitional cough,

accessory muscles also show greater activity. Despite the stronger and faster muscle activation associated with reflexive cough, the mean peak expiratory cough flow (PECF) has been shown to be higher with volitional cough.⁵¹ To date, no studies have differentiated characteristics of reflex versus spontaneous cough in individuals with ALS. However, based on clinical experience and reports of voluntary cough dysfunction in other clinical populations,⁴⁹ it is estimated that spontaneous cough may be stronger and preserved longer than voluntary cough in individuals with MND.

Recently more debate has emerged over placing cough, and other motor functions, into strictly reflexive versus volitional categories. Some would argue generally that the issue of reflex versus volition is not truly dichotomous, but rather a continuum.⁵² Similarly, in 2009 Eccles proposed a model that acknowledges difficulties with placing cough strictly into reflexive versus volitional categories.⁵³ In this model, cough is classified into three categories based on hypothetical central control mechanisms: 1) reflex cough – brainstem mediated; 2) voluntary cough-involving cortical control; and 3) “evoked” cough – a cough preceded by an urge to cough – involving an overlap of cortical control and brainstem control.^{53,54} Hegland and colleagues subsequently demonstrated that healthy individuals are able to modify their reflexive cough response to a level of stimulus where suppression of cough is not possible.⁵⁴ Based on this finding, Hegland presented an updated model of cough, based on Eccles work, indicating the possibility of exerting volitional control over reflexive cough. Cortical involvement during volitional cough includes sensorimotor activation along the Sylvian fissure, and activation in a pontine-mesencephalic region.⁵⁵ Mazzone and colleagues studied cortical involvement associated with evoked cough.⁵⁶ Evoked cough involved cortical activation in multiple regions, including posterior insula and posterior cingulate cortex.⁵⁶ Effort to suppress evoked cough was associated with activity in the anterior insula, anterior mid-cingulate cortex and inferior frontal gyrus.⁵⁶

Dystussia in motor neuron disease (MND)

Inability to effectively cough is referred to as “dystussia.” Dystussia is common in individuals with motor neuron disease. Contributing factors include respiratory impairments and laryngeal dysfunction. Respiratory dysfunction associated with MND may occur due to impairments of the respiratory musculature,³¹ and/or weakness of bulbar muscles that are needed to maintain airway patency. Dystussia is one of several complications of respiratory muscle weakness; others include respiratory failure, dyspnea and orthopnea.^{31,57}

Dystussia associated with MND contributes to risk for aspiration and respiratory failure. Due to progressive dysphagia, individuals with MND experience difficulty with secretion and saliva management. Inability to adequately clear secretions, owing to dystussia, is a contributing risk factor for aspiration and respiratory failure. Inability to clear these secretions contributes to potential airway obstruction that can interfere with breathing and with the individual’s potential to benefit from other respiratory aids, such as non-invasive ventilation.⁹ Dystussia can occur for different reasons in those with primarily bulbar versus primarily limb involvement. For individuals with limb involvement primarily, cough strength is affected most often by weakness of inspiratory and expiratory respiratory musculature. Those with primarily bulbar involvement, however, may have relatively normal function of the inspiratory and expiratory musculature. Dystussia in this group can occur due to weakened bulbar muscles and vocal folds. For instance, TVF weakness may result in reduced coordination of the muscular responses with airflow, and an inability to build-up adequate subglottic pressure and maintain upper airway patency during cough attempts.⁵⁸

Laryngeal dysfunction commonly occurs in bulbar ALS, but the patterns of abnormality are variable. Perceptual voice quality changes associated with ALS may be characterized by strain, harshness, breathiness, reduced volume, tremor and/or *flutter* (rapid oscillation

tremor).⁵⁹⁻⁶² Despite these changes, many with ALS can phonate late into the course of their disease.¹⁶ Variability has also been noted in patterns of abnormal TVF movements, with the following patterns reported: incomplete adduction, bowing, hyperfunction, and reduced abduction.¹⁷ Laryngospasm and glottic narrowing have also been reported in bulbar ALS.^{63,64} Hillel & Miller reported that approximately 30% of people with bulbar ALS present with impaired TVF abduction and passive paradoxical movements of the TVFs late in the course of the disease.¹⁶ A histochemical study revealed atrophic fibers in laryngeal musculature of people with ALS, with particularly severe neurologic changes in the posterior cricoarytenoid muscle, the major TVF abductor.⁶⁵ TVF dysfunction can have an obstructive effect on airflow during breathing. For instance, flow plateaus suggestive of airway narrowing and saw-tooth like flow oscillations suggestive of intermittent changes in upper airway caliber were reported for persons with bulbar involvement neuromuscular disease, including ALS.⁶⁶ Weakness or spasms of the laryngeal musculature may result in reduced airway patency due to laryngospasm or paradoxical movements of the vocal folds.^{58,64} However, to date, no studies have directly measured the relationship between TVF movements and cough dysfunction in bulbar ALS.

Methods for measuring laryngeal kinematics during cough

It is essential to develop tools for measuring TVF movements associated with cough that are clinically efficient and accessible, as this will aid further research efforts and eventual translation to clinical practice. While electromyography (EMG) provides valuable information, it is invasive and technically difficult to access some of the laryngeal muscles associated with cough using EMG wires, particularly the posterior cricoarytenoid. A solution to this problem is to use methods established for clinical measurement of TVF function during phonation to measure TVF function during cough. The following techniques have been successfully applied to the measurement of TVF movement during phonation: 1) use of laryngeal endoscopy video images

to measure maximum angle and angular velocity of the TVFs; 2) use of photoglottography to reflect glottic area; and 3) development of a visual perceptual rating scale to judge adequacy of key TVF movements observed from laryngeal endoscopy images. TVF angle and angular velocity have been measured from laryngeal endoscopy video of the TVFs during phonatory and swallowing tasks.⁶⁷⁻⁶⁹ Recently, Britton and colleagues demonstrated utility and reliability with measures of TVF angle and angular velocity in the context of volitional cough.⁴⁰

Photoglottography (PGG) is a technique that uses a photosensor taped to the cricothyroid membrane to transcutaneously measure changes in transglottic illumination with light emitted by the laryngeal endoscope. PGG measures have been correlated with changes in glottic area during phonation.⁷⁰ Visual perceptual rating scales have been used extensively for evaluation of vibratory patterns observed during phonation.^{71,72} However, few studies have used scales to rate the more gross TVF gestures of abduction and adduction.^{73,74} Visual perceptual rating scales have not previously been used to measure TVF movements during cough. Measures of maximum TVF angle and angular velocity were used in this project to examine TVF movements during cough in people functioning normally and with bulbar MND.

Purpose

No studies to date have examined cough-related TVF kinematic measures in individuals with MND. While it is well known that PEFV declines in MND,^{12,75,76} other cough-related airflow measures, i.e., expiratory phase rise time (EPRT) and volume acceleration (VA), have not been reported for individuals with MND. Some researchers suggest that EPRT reflects TVF function.⁷⁷ For these reasons, one purpose of this study is to examine group differences between TVF kinematic and airflow measures during volitional cough. In addition, the adequacy of laryngeal and supraglottic closure during the compression phase of cough in MND will be examined.

No prior studies have evaluated the relationship between extent and speed of TVF movements during the cough sequence and cough-related airflow measures. Because of the potential clinical implications of this relationship, a primary purpose of this research is to examine the laryngeal contribution to volitional cough dysfunction in bulbar MND. It is hypothesized that cough effectiveness (as measured by cough-related airflow) is associated with measures of TVF kinematics and timing in people with bulbar MND even after controlling for important cough-related variables.

Specific research questions are:

- 1) Are there group (MND versus control) differences between airflow and TVF kinematic measures during volitional cough? Specifically, are there group differences in:
 - a. cough-related airflow measures, including PEF, EPRT and VA?
 - b. maximum TVF abduction during the pre-compression inspiration and post-compression expulsion phases of cough?
 - c. average TVF velocity during the pre-compression inspiration and post-compression expulsion phases of cough?
- 2) Are there group differences in the pattern of TVF and supraglottic closure during compression phase of cough?
- 3) Is there preliminary evidence to support associations between cough-related airflow measures and measures of TVF kinematics? Specifically,
 - a. Is the maximum post-compression TVF abduction angle associated with PEF?
 - b. Is the post-compression TVF abduction angular velocity associated with EPRT?

CHAPTER II: METHODS

The primary purpose of this dissertation is to examine the laryngeal contribution to volitional cough dysfunction in bulbar MND. Approval was granted for this study from the University of Washington Institutional Review Board (IRB #39692; Committee B).

Study design

An observational study design was used to examine the relationship between cough-related airflow measures and cough-related TVF kinematic and timing measures in participants with bulbar MND and normal controls during a volitional cough task. Table 2 contains a list of variables that were included.

Table 2. Study variables

	Variable	Measurement units
Cough-related airflow	Peak expiratory cough flow (PECF)	liters/second (L/s)
	Expiratory phase rise time (EPRT)	seconds (s)
	Volume Acceleration (VA)	L/s/s
TVF Kinematics	Maximum pre- & post-compression TVF abduction angle (inspiration & expulsion phases)	degrees
	Minimum TVF adduction angle (compression phase)	degrees
	Pre-compression (inspiration phase) TVF Adduction angular velocity	degrees/s
	Post-compression (expulsion phase) TVF Abduction angular velocity	degrees/s

Participants

Participants with MND were recruited from patients at the University of Washington Medical Center, Seattle, Washington via rehabilitation, neurology and otolaryngology clinics.

Inclusion criteria included diagnosis of definite or probable ALS, PBP or PLS by a neurologist and current involvement of bulbar musculature (determined by a rating of ≤ 11 on the bulbar subsection of the ALS Functional Rating Scale - Revised⁷⁸). Diagnosis of ALS was based on the El Escorial criteria.⁷⁹ Exclusion criteria included absence of bulbar involvement, and/or a history of pulmonary or laryngeal disease prior to onset of MND-related symptoms. Healthy volunteers within the same age range as MND participants without a history of neurological, swallowing or breathing disorders, were recruited from university staff and the local community.

Procedures

Following informed consent, participants with MND completed an interview for the following demographic information: age, sex, race, height, current ALS/MND symptoms, symptoms at onset of MND, date of diagnosis, date of initial symptoms and pertinent medical history.

As part of the nasolaryngeal endoscopy exam, participant's most patent nasal cavity was decongested using a 0.05% Afrin[®] solution administered via an atomizer. Lidocaine (4% solution) was administered for some participants (8/12 control and 1/12 ALS participants) to alleviate sensitivity associated with passing the scope. Approximately 2-3 minutes later, the KayPentax videonasal laryngoscope was introduced via the nares. Endoscopic images were recorded digitally.

Participants were instructed to perform three volitional single cough maneuvers. During this task, data were obtained simultaneously: 1) Airflow; and 2) Laryngeal endoscopy video of TVF movements. These procedures are outlined in Figures 5 and 6.

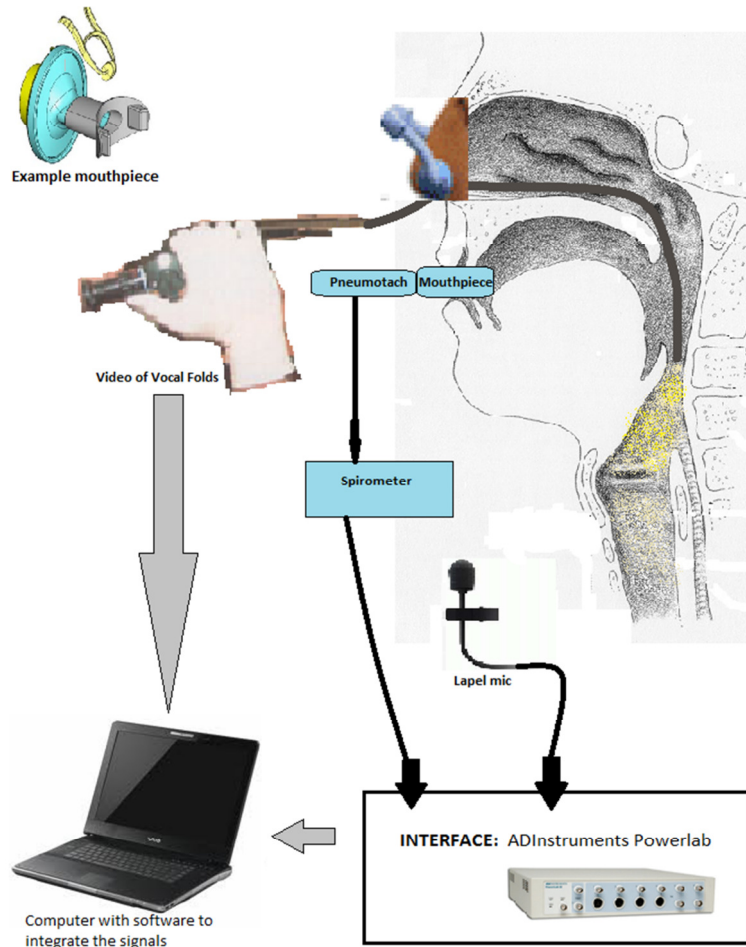


Figure 5. Diagram of methods of measurement

Simultaneous airflow was collected via a Hans-Rudolph Model 3813 pneumotach (Hans Rudolph, Inc., Shawnee, KS) and ADInstruments FE141 spirometer (ADInstruments, Inc., Colorado Springs, CO). To collect airflow data, a mouthpiece with an oral flange was placed in the participant's mouth and connected to the pneumotach and spirometer; a nose clip was used to occlude nasal airflow. The investigator visually inspected the adequacy of the lip seal to ensure there were no air leaks. The spirometer was calibrated prior to data collection. The spirometry signals were digitized at 2 kHz and displayed with ADInstruments, Inc., Labchart7 (Colorado Springs, CO) and temporally integrated with audio/video signals from laryngeal endoscopy.


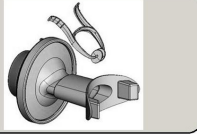
- 1) Subject's nostril is sprayed with 0.05% Afrin via an atomizer
- 2) A small lapel mic clipped to the shirt 
- 3) The Nasolaryngeal endoscope is placed
- 4) The mouthpiece and nose-clip are placed 
- 5) Subject is instructed to take a deep breath and cough hard (3 times)

Figure 6. Order of measurement procedures

Data analyses

The cough sample with the highest PECF was analyzed, except in cases where TVF movements were not well visualized from the video. In these cases, the coughs with adequate visualization of TVF movements were analyzed. If the cough data contained a cough epoch (e.g., due to participant difficulty with performing a single cough), the first cough of the sequence was analyzed.

Cough-related airflow

Cough-related airflow measures were used to measure cough effectiveness. The specific cough-related airflow measures used are indicated in Table 2 and Figure 7: PECF, EPRT and VA. PECF was measured directly via spirometry. EPRT was measured from the

continuous airflow wave form. VA was derived from EPRT and PECF measures, as indicated in Figure 7.

Inspiration phase: A to B
Compression phase: B to C
Expiratory phase Rise time (EPRT): C to D
Peak expiratory cough flow (PECF): D
"Volume acceleration" (VA): PECF / EPRT

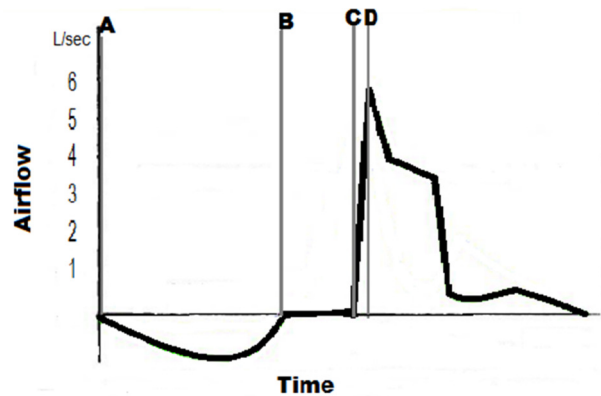


Figure 7. Volitional cough-related airflow measures

From Miller & Britton⁴⁶

TVF kinematic measures

TVF Angle: Measures of TVF angle are robust to changes in vantage point and provide an indication of airway patency. Video samples of inspiration and expulsion phases were rendered by frame to image sequences. For each frame in a given sequence, the TVFs were marked at the right and left vocal processes and anterior commissure by the primary investigator (Figure 8). From these marks, TVF angle was computed using custom software written with Matlab.⁶⁸ In instances where the epiglottis obscured the anterior commissure, the TVFs were marked from the vocal processes to the point where they could no longer be seen and the location of the anterior commissure was then computed as the intersection of the two lines. The TVF angle was measured on a total of 1695 frames; 11% of images were excluded due to inadequate visualization of the TVFs, e.g., > 50% of the TVFs being obscured by the epiglottis or by poor camera positioning, and/or blurring of the image which prevented accurate identification of laryngeal structures. The infraglottic aspect or pseudosulcus was marked as a surrogate of the TVFs on 2% of images where visualization of the TVFs was blocked by bulging

FVFs. The difference between the infraglottic aspect and the TVFs were measured on images for two participants (MND & control); differences were observed to vary between 0 and 12 degrees, with an average variance of 5 degrees; larger differences were seen with wider TVF abduction. Thus, in the instances where it was applied, it is estimated that marking of the infraglottic aspect slightly underestimated the TVF angle. As needed, frames before and after the image being marked were viewed to aid correct identification of laryngeal structures. Care was taken to avoid marking the posterior glottis. In images where the supraglottic structures were completely closing the airway, e.g., at the end of inspiration and beginning of expulsion, the TVF angle was marked as zero.

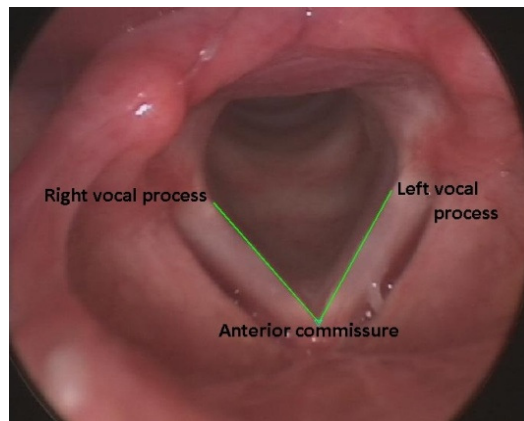


Figure 8. Vocal folds marked for angle computation in Matlab

TVF angular velocity: Measures of TVF angular velocity provide an indication of the speed and pattern of TVF movements during the end of inspiration phase pre-compression TVF adduction and the beginning of the expulsion phase post-compression abduction. The average velocity to reach the maximum TVF angle *within the pre-compression adduction and post-compression abduction regions* was calculated using the following equation:

$$\bar{v} = \Delta d / \Delta t$$

Average velocity is equal to the change in distance divided by the change in time.

The maximum TVF angle for pre-compression adduction was determined to be the maximum angle just prior to the pre-compression adduction. The maximum TVF angle for the post-compression adduction was determined to be the maximum TVF angle within +/- 0.15 second from the PECF. See Figure 9 for an illustration of these regions.

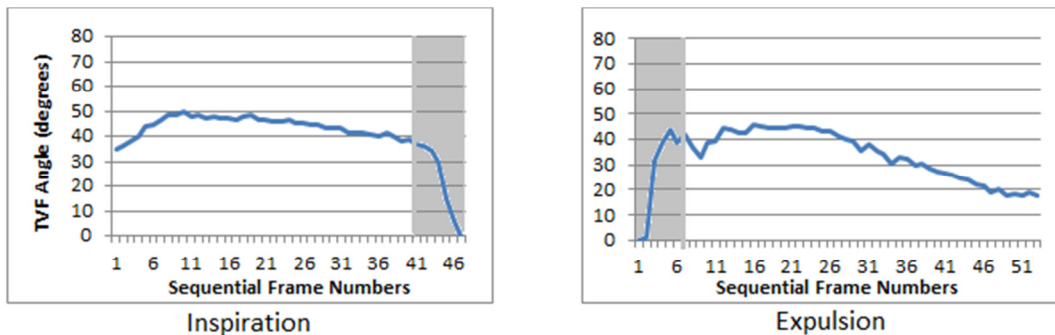


Figure 9. TVF angle measures: Regions of pre-compression adduction and post-compression abduction

Regions of pre-compression adduction (inspiration phase) and post-compression abduction (expulsion phase) are highlighted in gray.

Intra-rater and inter-rater reliability for sequential TVF angle measures: The methods for measurement of sequential and maximum TVF angles during the inspiration and expulsion phases of cough are identical to those published in the pre-dissertation study by Britton and colleagues.⁴⁰ In the Britton and colleagues study, intra-rater and inter-rater reliability for TVF markings of the vocal fold angles of young healthy participants was excellent, demonstrated by intra-class correlations of ≥ 0.97 . Because the populations in this study differed from Britton and colleagues, reliability measures were repeated. To examine intra-rater and inter-rater reliability for the sequential and maximum TVF angle measures, markings of the TVFs to calculate angles during inspiration and expulsion phases of cough were repeated by an experienced speech-language pathologist and/or otolaryngologist for at least 20% of participants. In addition, the PI completed at least 20% of the ratings twice with more than 24 hours between the rating sessions. Reliability, in terms of absolute agreement, of measuring the abduction angles and

the maximum abduction angles was analyzed with use of 2-way random model intraclass correlation coefficients (ICC).⁸⁰ The intra-observer ICC for 439 sequential angles and 12 maximum glottal angles measured from inspiration and expulsion phases of cough across 6 (3 controls; 3 MND) randomly selected participants by the PI were 0.99 (95% confidence interval [CI], 0.98 to 0.99) and 0.99 (95% CI, 0.99 to 1.0), respectively. The inter-observer ICC for 467 sequential angles and for 12 maximum glottal angles from inspiratory and expulsion phases of the 6 participants were 0.97 (95% CI, 0.96 to 0.98) and 0.99 (95% CI, 0.95 to 0.99), respectively.

Demographic and additional functional variables

Demographic data, such as age, height and sex was collected via interview. To estimate the contribution of respiratory muscle strength to cough related airflow measures, both maximum expiratory pressure (MEP) and maximum inspiratory pressure (MIP) were measured in addition to the simultaneous measures described above. For these measures, participants were required to insert a flanged mouthpiece orally and wear a nose clip. The mouthpiece was connected to a manometer; a small leak in the mouthpiece prevented inadvertent measurement of pressures generated intraorally. To measure MIP, participants were instructed to begin inspiratory effort at residual lung volume against a blocked airway. To measure MEP, participants were instructed to begin expiratory effort at total lung capacity, again against a blocked airway. Measures of forced vital capacity (FVC) were also collected with the spirometry equipment described earlier.

Ratings from the ALS Functional Rating Scale - Revised (ALSF_{RS}-R).⁷⁸ were collected for participants with MND in order provide an indication of current functional status and disease progression.

Statistical analyses

Descriptive analyses were performed for all variables. Independent-sample Student's t-tests were used to compare cough-related airflow and TVF kinematic variables by group. The significance level was set at $\alpha = 0.05$. No adjustments were made in the significance level for multiple comparisons in order to avoid eliminating potentially significant factors, as this study is exploratory in nature. Values reported in this study will require verification in larger studies. Associations between cough-related airflow and TVF measures (See Table 2 above) were analyzed via Pearson correlations.

CHAPTER III: RESULTS

Participants

Twelve participants (3 females, ages 54-76; 9 males, ages 45-71) with MND were recruited from patients at the University of Washington Medical Center, Seattle, Washington via rehabilitation, neurology and otolaryngology clinics. Twelve healthy volunteers (6 females, ages 41-68; 6 males, ages 56-66) and without a history of neurological, swallowing or breathing disorders, were recruited from university staff and the local community. All participants were Caucasian, except for one Hispanic male in the MND participant group. Descriptive characteristics of MND severity and onset are indicated below in Table 3.

Table 3. Motor neuron disease (MND) participants

Females

Code	Diagnosis	Age	ALSFRS-R Subscores ⁷⁸				Months post diagnosis	Months post ALS symptom onset	Location of first symptoms
			Bulbar	Fine Motor	Gross Motor	Respiratory			
A98	ALS	59	6	1	5	9	8	25	Bulbar onset: tongue & speech
A3	PLS	54	6	8	6	12	142	159	Spinal onset: legs
A35	ALS	76	5	9	8	10	4	22	Bulbar onset: speech

Males

Code	Diagnosis	Age	ALSFRS-R Subscores ⁷⁸				Months post diagnosis	Months post symptom onset	Location of first symptoms
			Bulbar	Fine Motor	Gross Motor	Respiratory			
A17	ALS	71	9	6	6	3	32	unknown	Spinal onset: hands and respiration
A10	ALS	71	9	9	10	10	12	14	Spinal onset: right hand
A16	PLS	53	8	8	6	9	25	63	Spinal onset: right foot drop
A76	ALS	60	7	7	7	11	7	17	Mixed onset: speech & right thumb
A24	PLS	59	8	9	6	8	133	205	Spinal onset: legs
A28	ALS	45	7	1	3	11	12	21	Spinal onset: arms twitching
A90	ALS	54	7	0	0	4	16	24	Spinal onset: right leg
A53	ALS	63	2	12	11	11	7	10	Bulbar onset: speech
A89	ALS	67	9	9	12	12	14	20	Mixed onset: Hand and speech

Descriptive group comparisons

Forced vital capacity (FVC)

FVC, in terms of the percentage of the predicted normal values for participants, is presented in order to provide descriptive statistics pertaining to participant's pulmonary function status. FVC measures were collected for all 12 MND and 12 control participants. The highest of three trials is reported. Each participant's predicted normal value was computed using prediction equations published by Hankinson and colleagues.⁸¹ Figure 10 displays FVC, in terms of percent predicted, for both groups. As expected, the MND group has lower FVC than controls.

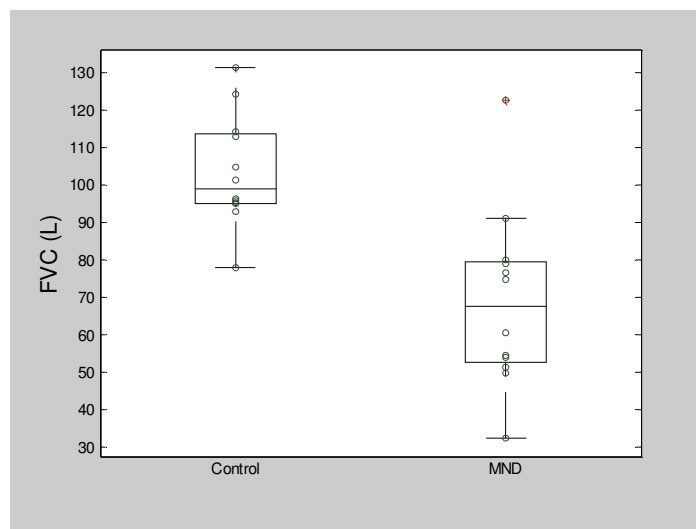


Figure 10. Forced vital capacity (percent predicted) -- Group comparisons

Boxes represent median and interquartile range. Whiskers extend to the lowest and highest data values within 1.5 times the interquartile range from the box edges. Any values located further than 1.5 times the interquartile range past box edges are indicated by asterisks. Circles indicate individual data points.

Slow vital capacity was collected for 7 MND participants who appeared to have possible airway obstruction with the FVC maneuver. In 5/7 of these participants, the slow vital capacity (completed after FVC) exceeded the highest FVC by an average of 0.19L (minimum 0.01 L; maximum 0.52 L).

Volume of air during inspiration and expulsion phases of cough

The volume of air during inspiratory and expulsion phases of cough is presented in order to provide further descriptive information. The volume of air during inspiration and expulsion phases of cough was derived from airflow data for all participants. All group comparisons were statistically significant: Inspiration volume $p=0.001$; Expulsion volume $p=0.02$. Figure 11 displays volume of air (liters) during inspiration and expulsion phases of cough for both groups. As expected, the volume of air during inspiration phase and during expulsion phase was lower in the MND group.

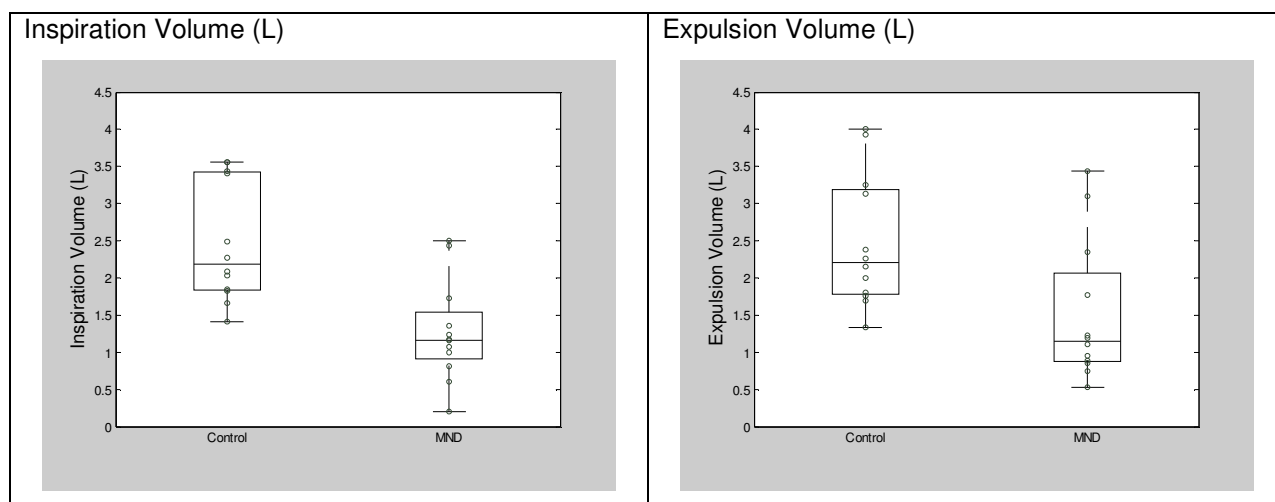


Figure 11. Volume of air during inspiration and expulsion -- Group comparisons
Boxes represent median and interquartile range. Whiskers extend to the lowest and highest data values within 1.5 times the interquartile range from the box edges. Any values located further than 1.5 times the interquartile range past box edges are indicated by asterisks. Circles indicate individual data points.

Maximum inspiratory pressure (MIP) and maximum expiratory pressure (MEP)

MIP and MEP measures are presented descriptively to provide further information regarding participant's pulmonary function status. MIP and MEP were collected for all participants. The highest of three trials is reported. Four of the MND participants had difficulty with lip seal on the MEP measures. In these instances, manual assistance was provided to aid adequacy of lips closure. Group data for MIP and MEP measures are displayed in Figure 12 below. As expected, MIP and MEP measures were lower in the MND group.

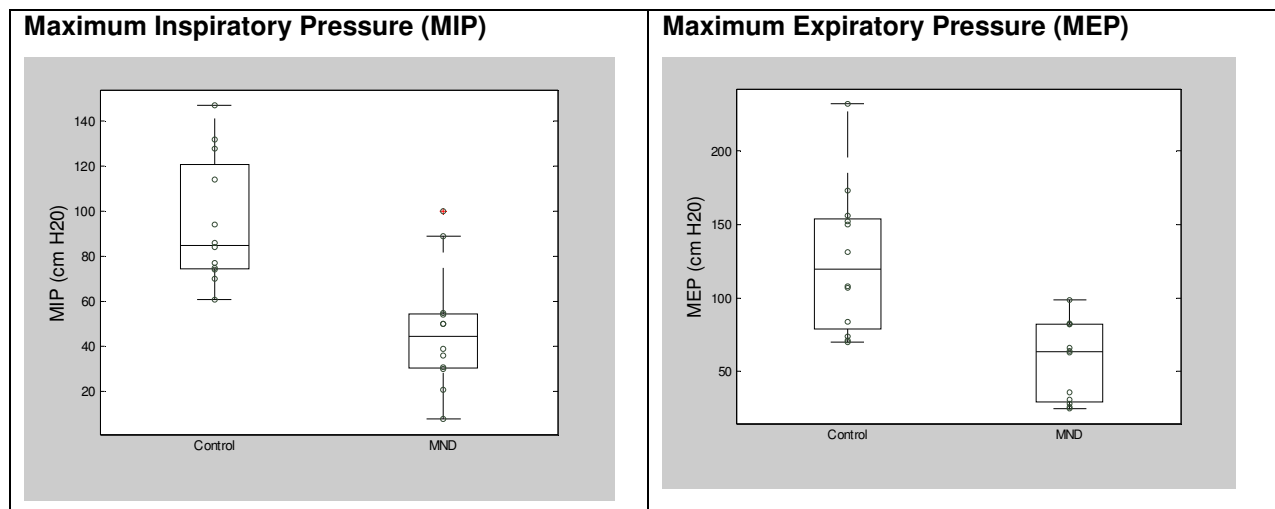


Figure 12. Measures of respiratory muscle strength -- Group comparisons

Boxes represent median and interquartile range. Whiskers extend to the lowest and highest data values within 1.5 times the interquartile range from the box edges. Any values located further than 1.5 times the interquartile range past box edges are indicated by asterisks. Circles indicate individual data points.

Duration of the phases of cough:

Duration data for each phase of cough is presented in order to compare control and MND groups. The duration of each phase of cough was derived from airflow data for all participants. Group comparisons were not statistically significant: Inspiration phase duration $p=0.13$; Compression phase duration $p = 0.77$; and Expulsion phase duration $p = 0.23$. Figure 13 displays durations for both control and MND groups across each phase of cough.

Descriptive statistics for duration of the phases of cough is outlined in Table 4.

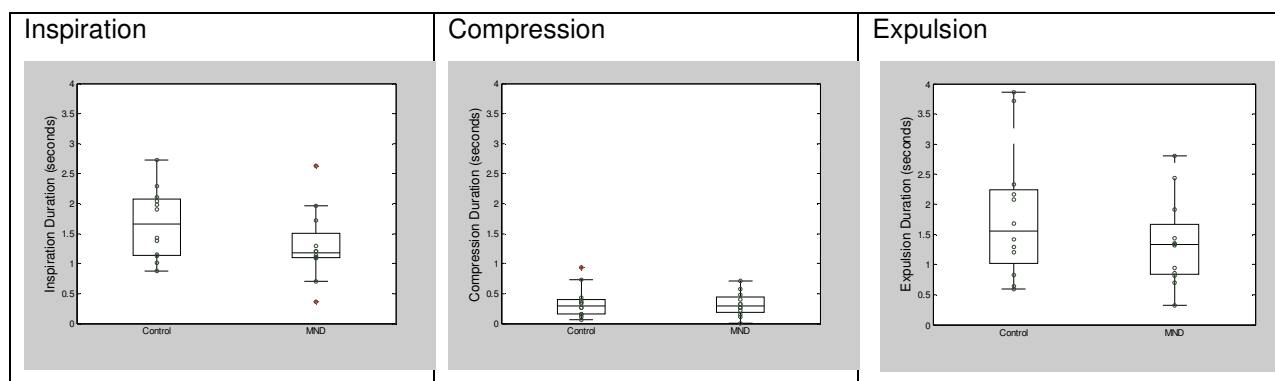


Figure 13. Duration of the phases of cough -- Group Comparisons

Boxes represent median and interquartile range. Whiskers extend to the lowest and highest data values within 1.5 times the interquartile range from the box edges. Any values located further than 1.5 times the interquartile range past box edges are indicated by asterisks. Circles indicate individual data points.

Table 4. Descriptive statistics for duration of the phases of cough

	Inspiration		Compression		Expulsion	
	Control	MND	Control	MND	Control	MND
Mean	1.67	1.29	0.35	0.32	1.82	1.35
SD*	0.58	0.59	0.25	0.20	1.08	0.72
Minimum	0.88	0.36	0.06	0.00	0.60	0.32
Maximum	2.73	2.63	0.93	0.71	3.86	2.80

Units = seconds; SD = standard deviation*

Otolaryngology Observations

Otolaryngology observations of abnormalities in laryngeal structure or function for the MND participants was tabulated. See these listed below in Table 5.

Table 5. Otolaryngology observations

Observation	Number of MND participants (of 12 total)
Mild or mild-moderate posterior cricoid edema	9
Excessive saliva in pyriform sinuses	9
Quivering of the arytenoids or TVFs	8
Bowing of the TVFs	6
Asymmetry	3
Gagging	3
Reduced TVF abduction	3
Swelling of the FVFs	2
Paradoxical TVF movements during inspiration	2
Unilateral TVC immobility	1

Cough-related research findings

Simultaneous collection of laryngeal endoscopy and airflow data was completed for all participants. Most of the participants tolerated this well. However, efforts to collect simultaneous laryngeal endoscopy and airflow data for two MND participants were hampered

due to significant gagging; both participants tolerated data collection of the measures separately. Squeezing of the pharyngeal walls was informally observed with 5/12 MND and 3/12 control participants following placement of the mouthpiece. In some of these participants, the squeezing of the pharyngeal walls restricted visualization of the TVFs during expulsion phase of cough.

Analyses were completed on the cough sample with the highest PEF, except in instances where visualization of the TVFs was inadequate. Visualization of the TVFs during the expulsion phase of cough on the cough sample with the highest PEF was inadequate for 2/12 MND and 5/12 control participants. In these instances, another cough sample with adequate laryngeal endoscopy visualization of the TVFs was used for the analysis. Laryngeal endoscopy data for two participants (1 male MND and 1 control) were omitted altogether due to inadequate visualization of the TVFs across all cough samples.

Cough-related airflow: Group comparisons

This section summarizes results for research question #1a: *“Are there group differences between cough-related airflow measures, including PEF, EPRT and VA?”* In order to compare cough effectiveness between the groups, expulsion phase airflow during cough was analyzed for all participants: 12 MND (3 female; 9 male) and 12 control (6 female; 6 male). Statistically significant differences between MND and control participants were observed for all airflow measures: PEF ($p = 0.01$); EPRT ($p = 0.004$); and VA ($p = <0.001$). PEF and VA were significantly reduced in the MND group, when compared to controls. EPRT was significantly larger and more variable in the MND group, when compared to controls. Variability was larger for the MND group for EPRT and larger in the control group for VA. Figure 14 displays group comparisons for each of the cough-related airflow measures.

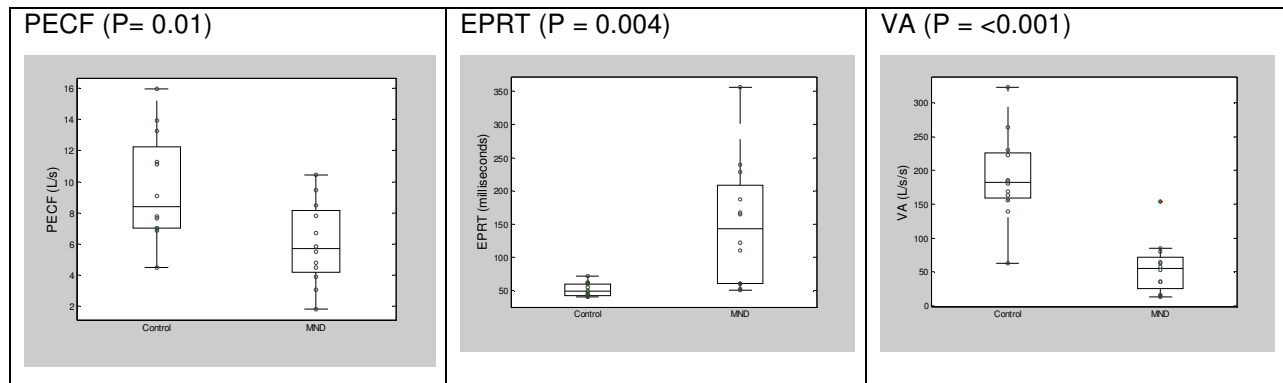


Figure 14. Group comparisons of airflow measures PECF, EPRT & VA during expulsion phase of cough

Boxes represent median and interquartile range. Whiskers extend to the lowest and highest data values within 1.5 times the interquartile range from the box edges. Any values located further than 1.5 times the interquartile range past box edges are indicated by asterisks. Circles indicate individual data points.

Maximum TVF abduction angles: Group comparisons

This section summarizes results for research question #1b: “Are there group differences between measures of maximum TVF abduction during the pre-compression inspiration and post-compression expulsion phases of cough?” In order to compare group differences in the extent of TVF abduction during cough, maximum TVF abduction angles were derived from sequential angle data during inspiration and expulsion phases of cough. A total of 44 video clips (separate video clips for inspiration and expulsion phases from each cough) were rendered to bitmap frames for analysis. Video data for 2 participants (1 male control and 1 male MND) were excluded due to inadequate visualization of the vocal folds during the expulsion phase of cough. Maximum TVF abduction angles were analyzed for 11 MND participants (3 female; 8 male) and 11 control participants (6 female; 5 male). Figure 15 compares maximum TVF angles for the pre-compression inspiration and post-compression expulsion (± 0.15 second of PECF) for both groups. No statistically significant group differences were observed for the maximum pre-compression TVF angle, occurring at the end of the inspiration phase just prior to TVF closure. However, group differences for the maximum TVF angle during the post-compression expulsion phase approached significance, with the MND group demonstrating smaller and more variable maximum TVF angles than controls.

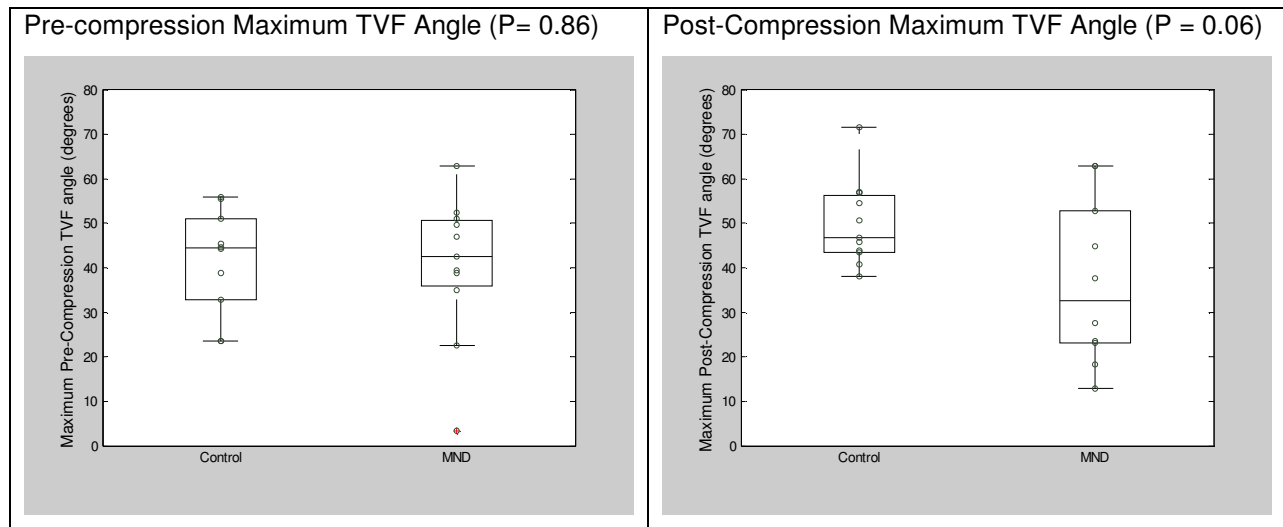


Figure 15. Group comparisons of maximum TVF pre- & post-compression angles

Boxes represent median and interquartile range. Whiskers extend to the lowest and highest data values within 1.5 times the interquartile range from the box edges. Any values located further than 1.5 times the interquartile range past box edges are indicated by asterisks. Circles indicate individual data points.

Average velocity of TVF movements

This section summarizes results for research question #1c: “Are there group differences in average TVF velocity during the pre-compression inspiration and post-compression expulsion phases of cough?” In order to compare group differences in the speed of TVF movements during cough, the average velocity of TVF movements was examined during pre-compression adduction and post-compression abduction. TVF angle average velocity for inspiratory phase pre-compression adduction was calculated for 11 MND (3 female; 8 male) and 11 control (6 female; 5 male) participants. For expulsion phase post-compression abduction, TVF angle average velocity was calculated for 10 MND (3 female; 7 male) and 11 control (6 female; 5 male) participants. Figure 16 displays the average TVF angle velocity for inspiratory phase pre-compression adduction and the expulsion phase post-compression abduction across both groups. No statistically significant group differences were observed for the inspiratory phase pre-compression adduction TVF angle average velocity. Group differences for the expulsion phase post-compression abduction TVF angle average velocity were statistically significant ($p =$

0.003). Thus, the average TVF velocity was similar between the groups during inspiration, but was slower for the MND group during expulsion phase of cough.

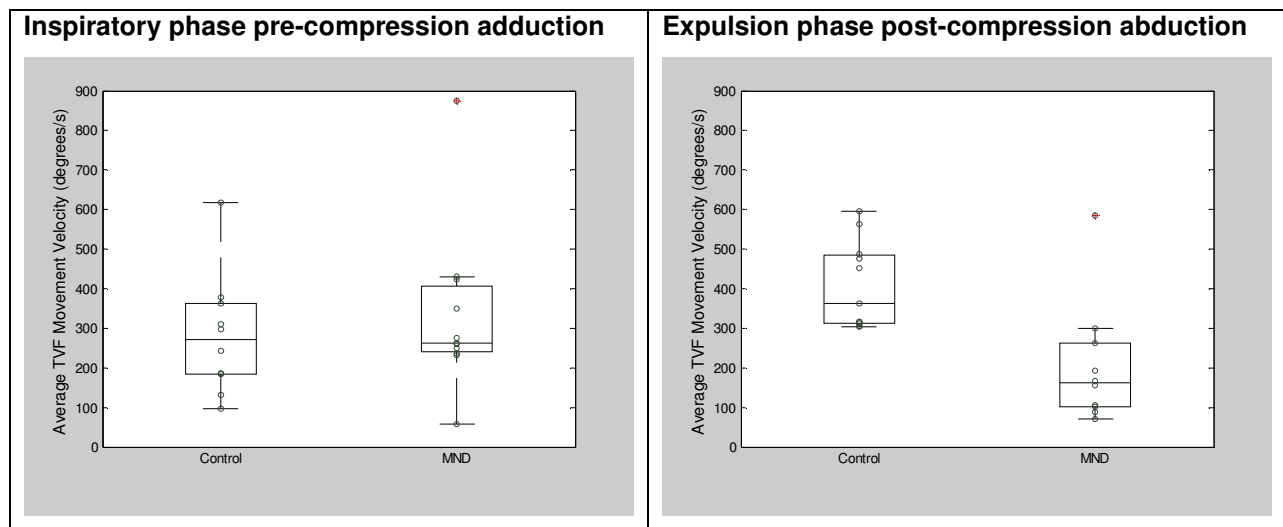


Figure 16. TVF angle average velocity

Maximum TVF angle or pre-compression adduction = maximum angle just prior to the pre-compression adduction. Maximum TVF angle for post-compression abduction = maximum TVF angle within +/- 0.15 second from the PECF. Boxes represent median and interquartile range. Whiskers extend to the lowest and highest data values within 1.5 times the interquartile range from the box edges. Any values located further than 1.5 times the interquartile range past box edges are indicated by asterisks. Circles indicate individual data points.

TVF and supraglottic closure during compression phase of cough

This section summarizes results for research question #2: *“Are there group differences in the pattern of TVF and supraglottic closure during the compression phase of cough?”*

Patterns of TVF and supraglottic closure during the compression phase of cough are presented in order to compare the adequacy of laryngeal closure during the compression phase of cough between the groups. Videos of cough for all participants (MND n=12; Control n=12) were observed for adequacy of TVF and supraglottic closure during the compression phase of cough. Figure 17 provides an example of supraglottic closure during the compression phase of cough. All of the MND and control participants had complete TVF closure during compression phase of cough. While supraglottic closure was complete in all control participants, it was incomplete in 2 of the MND participants.

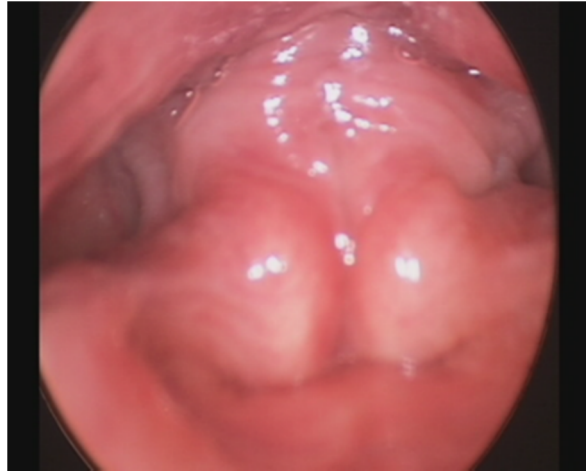


Figure 17. An example of supraglottic closure during the compression phase of cough

During compression phase of cough, supraglottic reinforcement of airway occurs through extreme anterior-posterior compression (i.e., arytenoids contacting the petiole of the epiglottis) and medialization of the false vocal folds.

Associations between PECF and maximum TVF angle

This section summarizes results for research question #3a: *“Is the maximum post-compression TVF abduction angle associated with PECF?”* In order to explore whether or not the maximum post-compression TVF angle during expulsion phase of cough might have an effect on PECF, analyses were completed to examine associations between these variables. Analysis for associations between PECF and the maximum TVF angle during +/- 0.15 second of the PECF was completed for 10 MND (7 male; 3 female) and 11 control (5 male; 6 female) participants. Two participants (1 male MND and 1 male control) were omitted from analysis due to inadequate visualization of the TVFs during the expulsion phase of cough. One additional MND participant was omitted due to inadequate visualization of the TVFs when measured simultaneously with airflow. Pearson correlation for MND participants demonstrated a strong positive relationship between PECF and maximum TVF angle which approached statistical significance, $r = 0.57$ ($p = 0.09$). Pearson correlation for control participants showed a negligible relationship and was not statistically significant, $r = 0.138$ ($p = 0.69$). Thus, PECF tended to correlate with maximum TVF angles in the MND group, but not for controls. Pearson correlation for all participants combined also showed a moderately strong positive relationship and was

statistically significant, $r = 0.493$ ($p = 0.02$), but this may be artifact due to the differences between groups (see Figure 18). Figure 18 displays a scatter plot illustrating the relationship between PEF and maximum post-compression TVF angle (within 0.15 second of PEF) for both groups.

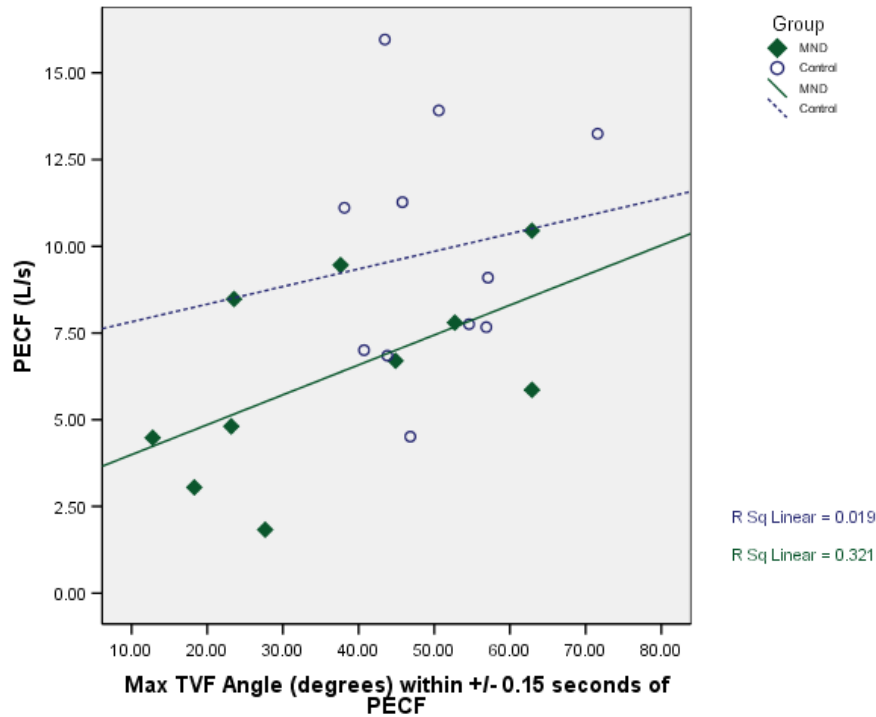


Figure 18. Associations between PEF and maximum TVF angle (within +/- 0.15 second of the PEF)

In order to further explore whether the association between PEF and maximum TVF angle might vary depending on the severity of bulbar symptoms, data for MND participants is graphically displayed by severity of bulbar symptoms, per ratings on the ALSFRS-R, bulbar subscale, for 10 ALS participants (7 male; 3 female). A score of 12 on the bulbar ALSFRS-R scale is equivalent with normal function, or no symptoms. In Figure 19 below, “mild” bulbar symptoms is equivalent with an ALSFRS-R bulbar scale rating between 9 – 11; “moderate” is equivalent with an ALSFRS-R bulbar scale rating between 6 – 8; and “severe” is equivalent with

an ALSFRS-R bulbar scale rating of ≤ 5 . Two of the 12 MND participants had ALSFRS-R ratings of ≤ 5 . One of these participants is not represented on the Figure 19 below due to inadequate visualization of the TVFs on the laryngeal endoscopy video. This particular participant demonstrated reduced TVF abduction and a max PEF of 5.51 L/s. No apparent trend associated with severity of bulbar symptoms was seen. While there is an association between PEF and maximum TVF angle within ± 0.15 s of PEF, the association between these two variables according to severity cannot be established because there are too few observations in each severity group. Therefore, differences in association between PEF and maximum TVF angle within ± 0.15 s of PEF according to severity of bulbar symptoms cannot be adequately inferred for lack of enough data in each severity group.

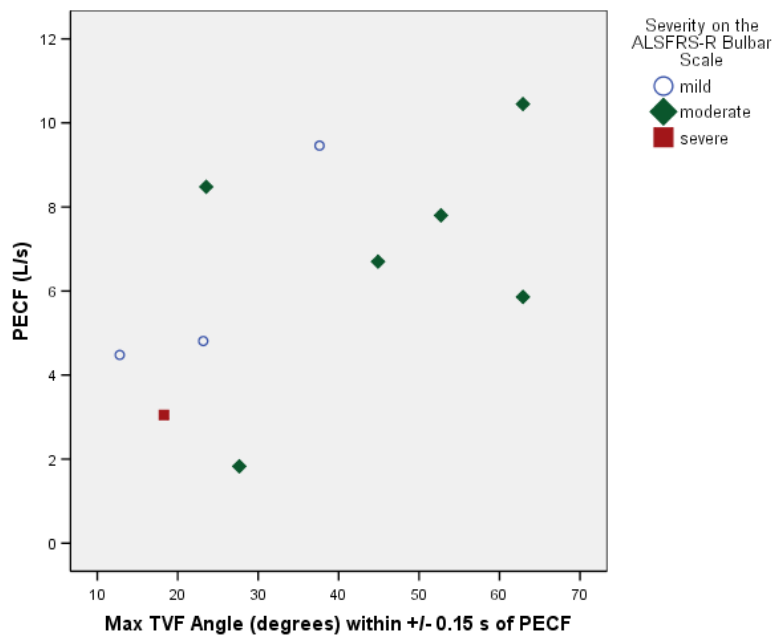


Figure 19. Associations between PEF and maximum TVF angle (within ± 0.15 second of PEF): MND participants grouped by severity of bulbar symptoms

Associations between EPRT and TVF abduction average velocity

This section summarizes results for research question 3b: *“Is the post-compression TVF abduction angular velocity associated with EPRT?”* In order to explore whether or not the TVF

abduction average velocity during expulsion phase of cough has an effect on EPRT, analyses were completed to examine associations between these variables. Analysis for associations between EPRT and the TVF abduction average velocity was completed for 10 MND (3 female; 7 male) and 11 control (6 female; 5 male) participants. Two participants (1 MND and 1 control) were omitted from analysis due to inadequate visualization of the TVFs during the expulsion phase of cough. One additional MND participant was omitted due to inadequate visualization of the TVFs when measured simultaneously with airflow. Pearson correlations for MND participants showed a moderately strong negative relationship ($r = -0.485$, $p=0.16$) and for control participants showed a moderately negative relationship ($r = -0.339$, $p = 0.31$); however, neither were statistically significant. For all participants combined, Pearson correlation was significant, $r = -0.663$, $p = 0.001$, and demonstrated a strong negative relationship. Thus, there was a strong, statistically significant, relationship between EPRT and TVF abduction average velocity when the groups were combined, but not separately. However, as seen in Figure 20 below, there is most likely artifact in this association of all participants combined due to the difference in the distribution of the two variables according to group. Figure 20 displays a scatter plot illustrating the association between EPRT and TVF abduction average velocity for both groups.

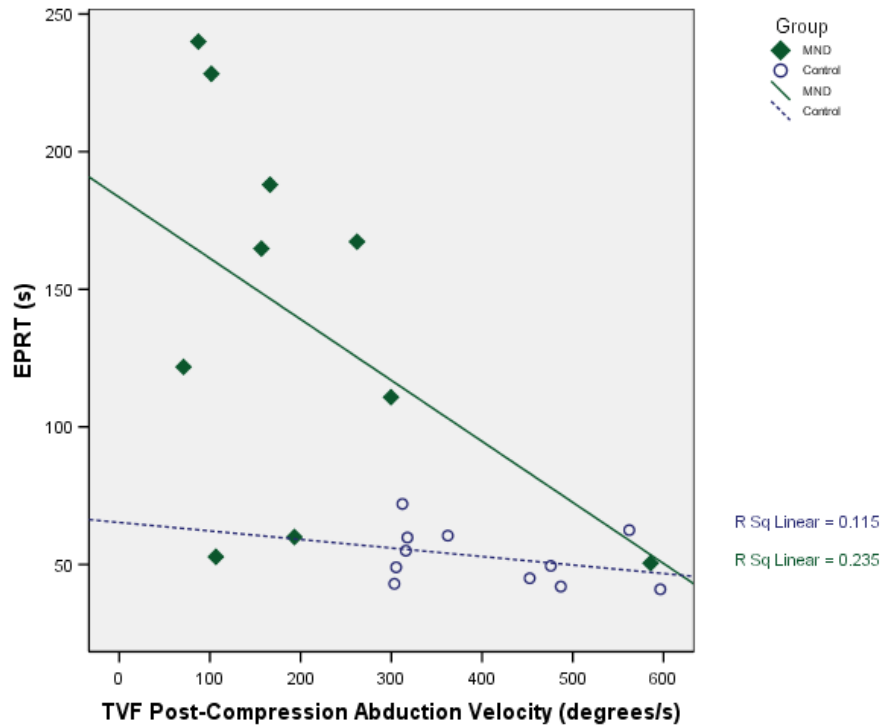


Figure 20. Associations between EPRT & TVF post-compression abduction average velocity

In order to further explore whether the association between EPRT and TVF post-compression TVF abduction velocity might vary depending on the severity of bulbar symptoms, data for MND participants is graphically displayed by severity of bulbar symptoms, per ratings on the ALSFRS-R, bulbar subscale, for 10 ALS participants (7 male; 3 female). A score of 12 on the bulbar ALSFRS-R scale is equivalent with normal function, or no symptoms. In Figure 21 below, “mild” bulbar symptoms is equivalent with an ALSFRS-R bulbar scale rating between 9 – 11; “moderate” is equivalent with an ALSFRS-R bulbar scale rating between 6 – 8; and “severe” is equivalent with an ALSFRS-R bulbar scale rating of ≤ 5 . Again, no clear trend associated with level of bulbar symptom severity, as measured by the ALSFRS-R, is observed.

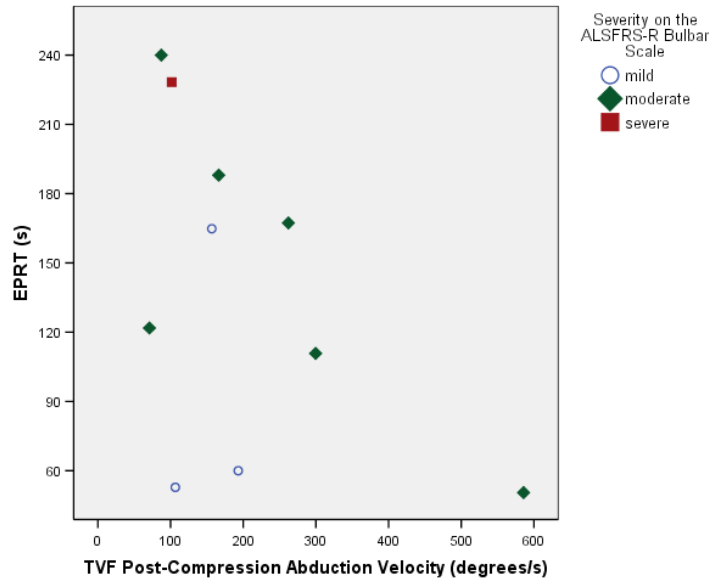


Figure 21. Associations between EPRT and TVF post-compression abduction velocity: MND participants grouped by severity of bulbar symptoms

Individual Findings & Cases

Individual participant descriptive statistics for a selected number of key variables are presented below in Table 6. Aside from FVC and MEP, normal values are unknown for the measures indicated below. In order to more effectively compare participants, data was shaded gray based on a gross estimate of abnormality. Criteria for judging normality is based on prior research and/or observations from control participant data in this study. Specific criteria used to grossly indicate abnormality for each variable is indicated below Table 6.

Table 6. Descriptive statistics of selected measures across participants

SUBJECT CODE	FVC (% Predicted)	MEP (cmH ₂ O)	MAX PCEF (L/s)	EPRT (ms)	Supraglottic closure during compression?	Maximum TVF Angle within +/- 0.15 s PCEF	Expulsion Abduction Velocity to Maximum Angle +/- 0.15 s PCEF
MND PARTICIPANTS							
A17	51.34	31	4.81	60.00	Y	23.17	193.11
A10	76.53	83	9.46	164.80	Y	37.62	156.76
A16	122.68	99	10.45	167.30	Y	62.90	262.09
A76	49.59	66	6.70	188.00	Y	44.89	166.24
A24	78.94	82	7.80	50.50	Y	52.72	585.74
A28	91.00	82	8.48	240.00	N	23.54	87.19
A90	32.40	25	3.90	61.00	Y	N/A	N/A
A98	80.08	36	5.86	110.80	Y	62.91	299.57
A3	60.51	28	1.83	121.80	N	27.65	70.89
A53	54.35	64	5.51	356.00	Y	N/A	N/A
A89	74.79	63	4.48	52.80	Y	12.79	106.57
A35	53.82	26	3.05	228.30	Y	18.29	101.61
CONTROL PARTICIPANTS							
C44	101.37	156	15.961	60.5	Y	43.47	362.27
C53	94.96	74	4.5126	72	Y	46.83	312.19
C96	95.13	131	7.0057	45	Y	40.72	452.49
C75	114.24	107	6.8476	42	Y	43.81	486.83
C3	95.79	84	7.6694	55	Y	56.87	315.94
C46	124.25	150	11.273	49	Y	45.79	305.27
C78	104.76	108	7.7544	43	Y	54.60	303.33
C48	131.19	232	13.246	41	Y	71.58	596.47
C54	96.36	71	7.0088	41.5	Y	N/A	N/A
C30	92.92	70	9.0947	49.5	Y	57.10	475.80
C87	112.84	173	11.11	59.8	Y	38.12	317.70
C4	77.94	152	13.917	62.5	Y	50.60	562.24

In order to indicate a gross approximation of abnormality (shaded gray above) the following values are use:

FVC (percent predicted): $\leq 75\%$ of the predicted normal.

MEP (cmH₂O): Values below the means reported below. Definitive norms have not been determined for MEP. The following summarizes what is currently known about expected values for MEP:

- For adults 18 to 65 years old, the mean MEP for men is 140 cm H₂O and 95 cm H₂O for women.⁸²
- For adults 65 to 85 years old, the reference range for MEP is 140 to 190 cm H₂O in men and 90 to 130 cm H₂O in women.⁸²

PECF: <500 L/s, as used by Toussaint et al.⁸³

EPRT: <67 ms. Smith-Hammond and colleagues⁴ report that an EPRT of >67 ms correctly identified >90% of aspirators in individuals status post stroke.

Max TVF Angle and Expulsion Abduction Velocity: 2 SD below the mean of the control group.

Two cases are described below to illustrate the types of impairments that can occur, as it is difficult to capture individual variability in group data.

Case #1

“Case #1” (A28) is a 45 year old male (identical twin) who had been diagnosed with ALS a year prior to participation with this study. His initial symptoms were characterized by twitching in his arms nearly 2 years prior. His ALSFRS-R subscore ratings on the day of participation in this study were: Bulbar 7/12; Fine motor 1/12; Gross Motor 3/12; and Respiratory 11/12. Despite significant involvement of his limbs, this participant’s FVC was 91% of the predicted value. His slow vital capacity was slightly larger (an improvement of 0.15 L). His best of three MIP and MEP measures were 100 cmH₂O (within normal limits) and 82 cmH₂O (mildly impaired), respectively. Prior to the onset of ALS, he had no neurological, pulmonary or laryngeal impairments, except for removal of laryngeal polyps 6 years prior to the diagnosis of ALS.

Otolaryngology observations from laryngeal endoscopy included significant impairments of TVF abduction, paradoxical TVF movements during inspiration and sniff abduction, mild quivering of the arytenoids and TVF bowing. See impairments of TVF abduction during cough in Figure 22. Despite these impairments, this participant’s vocal quality was good with no perceptible hoarseness or strain and he had no complaints of difficulty with breathing.

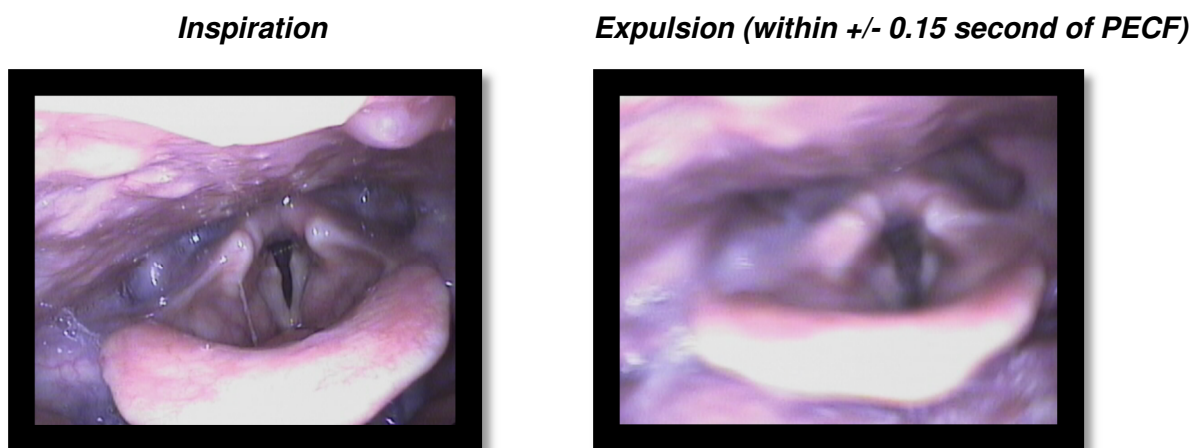


Figure 22. "Case #1": Severely impaired maximum TVF abduction observed during inspiration and expulsion phases of cough

Paradoxical TVF movements were observed in this participant to the point of TVF closure during the inspiratory phase of cough. This might have resulted in airway obstruction if it were not for opening of the posterior glottis. In this participant, during inspiratory phase of cough, the posterior glottis was open in context of approximated TVFs for 37 of the 51 frames during inspiration. See Figure 23 below for images of an open posterior glottis in the context of approximated or closed TVFs during inspiration phase of cough. The participant did not complain of difficulty with inspiration.

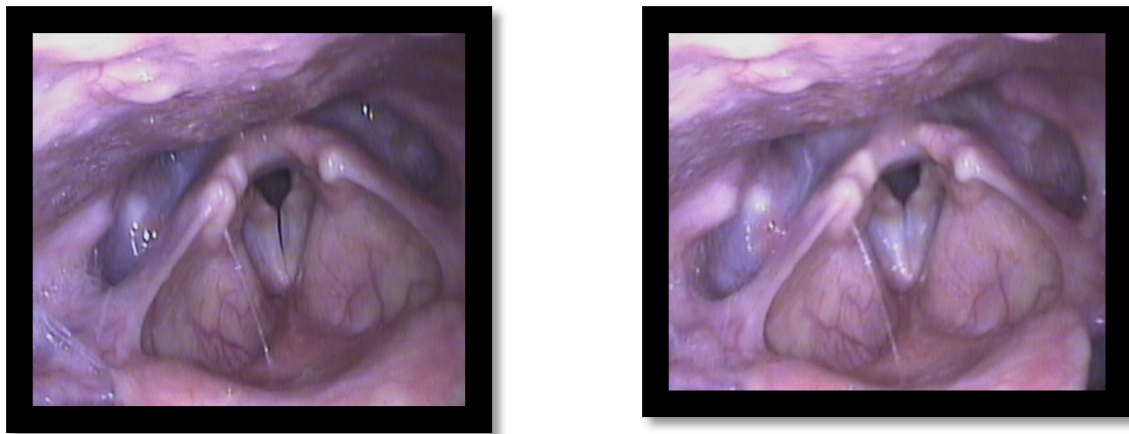


Figure 23. "Case #1": Open posterior glottis in the context of closed or approximated TVFs during the inspiratory phase of cough with paradoxical TVF movements

During the compression phase of cough, "Case #1" demonstrated adequate TVF closure, but incomplete supraglottic closure. As indicated above, in this study, 10/12 MND and all control participants demonstrated complete TVF and supraglottic closure during the compressive phase of cough. The maximum PECF was 8.48 L/s, well within what is considered to be normal limits. However, his EPRT and VA were 240 ms and 35.34 L/s/s for the same cough. Comparatively, the mean EPRT and VA for control participants in this study were 51.73 ms (SD 10.13 ms) and 189.93 L/s/s (SD 65.43 L/s/s), respectively. In prior studies, differences with EPRT and VA have been associated with higher risk for aspiration.^{3,8}

See Figure 24 for a graph of airflow data and sequential TVF angles during inspiration and expulsion phases of cough. This participant's sequential TVF angles grossly mirror what is

observed in airflow data. Increased airflow instability is observed compared with normal participants, as well. Airflow instability also occurs during times when the TVFs are approximated or nearly closed.

Clinical implications for "Case #1": Without assessment through laryngeal endoscopy, it would have been impossible to diagnose the inadequacy of TVF abduction and paradoxical TVF movements in this participant. This participant had no subjective complaints related to his voice or breathing. His voice quality was adequate. Routine pulmonary function tests also would not identify a potential problem, as his PEFV and FVC were within normal limits. EPRT and VA are not typically included in routine pulmonary function tests. However, these measures provided a clear indication of impairments, and EPRT may potentially suggest TVF involvement.

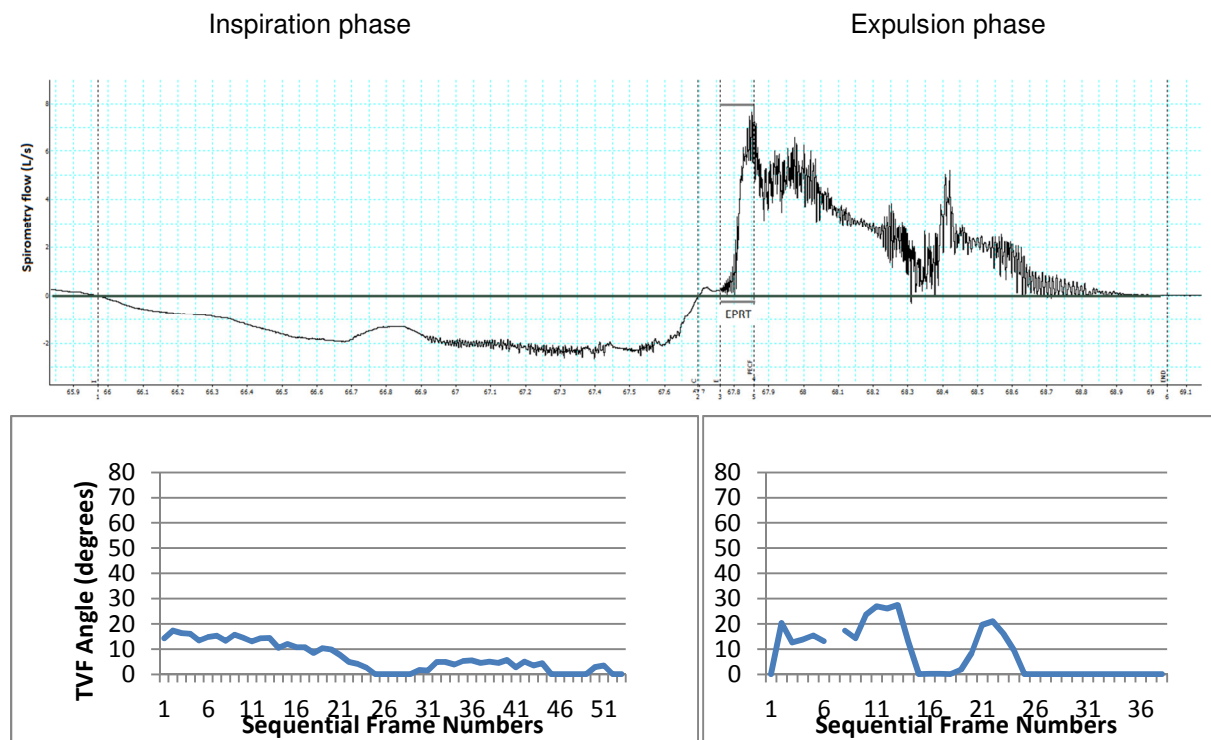


Figure 24. Simultaneous airflow and sequential TVF angle measures during inspiration and expulsion phases of cough for "Case #1"

In the airflow trace, inspiration is below the zero line, and expiration is above the zero line. Dotted lines mark the beginning of the phases of cough as well as the PEFV and end of expiration phase. The EPRT (240 ms) is indicated. Frame-by-frame sequential angle measures from video collected simultaneously with this cough sample are displayed below the airflow trace.

Case #2

“Case #2” (A3) is a 54 year old female who was diagnosed with PLS approximately 12 years prior to participation in this study. Her initial symptoms involved weakness in her legs. Her ALSFRS-R subscore ratings on the day of participation with this study were: Bulbar 6/12, Fine motor 8/12, Gross Motor 6/12 and Respiratory 12/12. Her best FVC was 61% of the predicted value, adjusted for her age, height and gender. Her best of three MIP and MEP measures were 36 and 28, both well below normal ranges. Prior to the onset of PLS related symptoms, she had no neurological, pulmonary or laryngeal impairments. No significant laryngeal impairments were observed by an otolaryngologist examining the video collected for this study, except for mild edema around the cricoid/inter-arytenoid region. She demonstrated adequate TVF mobility and range of motion. Her vocal quality, however, was characterized by low volume, mild-moderate strain and hyper-nasal resonance.

The maximum PECF for “Case #2” was 1.83 L/s. Her EPRT and VA were 121.8 ms and 15.04 L/s/s for the same cough. In this case, all of the cough-related airflow numbers fall within an abnormal range. In Figure 25 below, also note the slowness of TVF movements during the expulsion phase of cough. Unlike all control participants, she demonstrates no peak of TVF movements that coincide with the PECF. Her overall maximum TVF abduction during expulsion phase of cough is 71.5 degrees, while the maximum TVF abduction that occurs within +/- 0.15 second from PECF is 27.65 degrees. Therefore, while her TVF mobility and extent of abduction appear normal on an otolaryngology exam, the speed of movement is abnormally slow. In addition, similar to “Case #1” above, she also demonstrated incomplete supraglottic closure during the compression phase of cough.

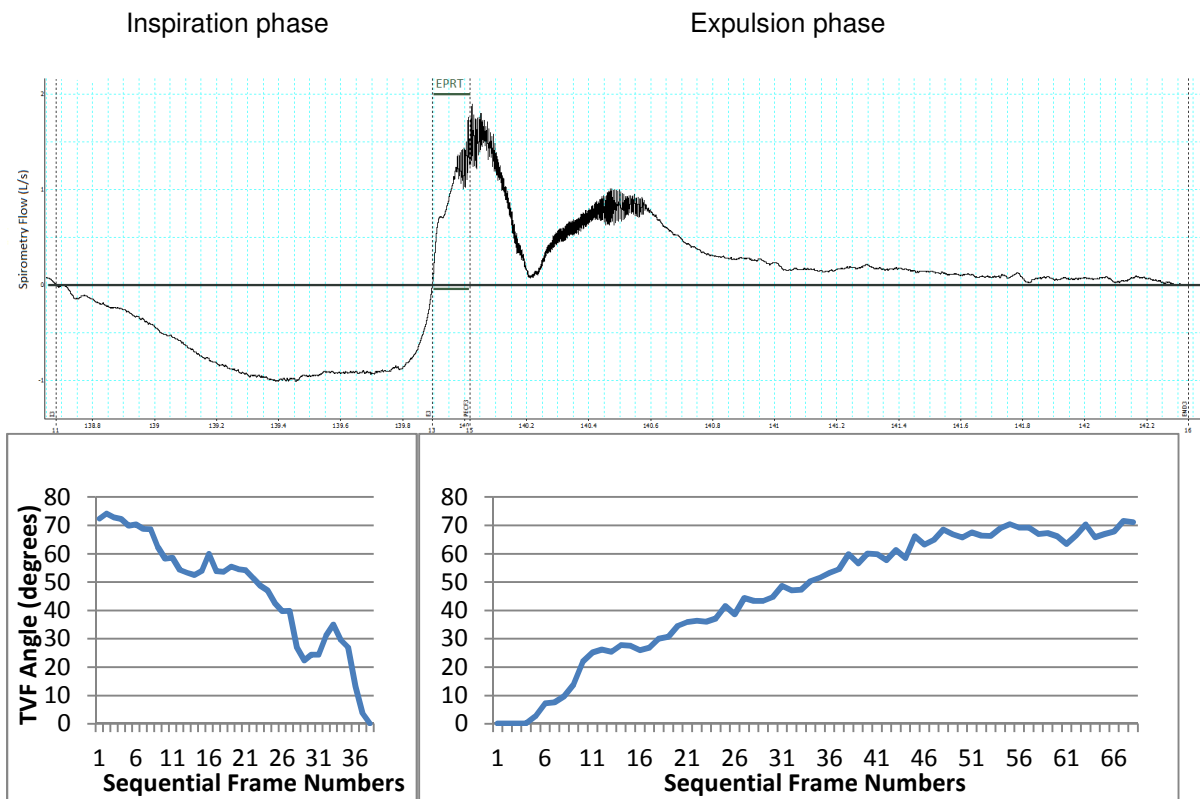


Figure 25. Simultaneous airflow and sequential TVF angle measures during inspiration and expulsion phases of cough for "Case #2"

In the airflow trace, inspiration is below the zero line, and expiration is above the zero line. Dotted lines mark the beginning of the phases of cough as well as the PECF and end of expiration phase. The EPRT (121.8 ms) is indicated. Frame-by-frame sequential angle measures from video collected simultaneously with this cough sample are displayed below the airflow trace.

Clinical implications for "Case 2": Despite a completely adequate extent of TVF mobility, the speed of TVF abduction movement in Case 2 is extremely slow – rendering TVF function during cough inadequate for a productive cough. Supraglottic closure during the compression phase of cough was also slow and incomplete. In Figure 25 above, there is a complete absence of a peak in the post-compression TVF abduction associated with the PECF. In contrast, all control participants demonstrated an initial peak in TVF abduction within +/- 0.15 second of the PECF. The slowness of movement is also apparent in her respiratory muscles and other volitional bodily movements, and is most likely related to increased muscle tone of spasticity common with UMN degeneration in PLS. Since her TVF muscles appear adequate and overall range of movement is adequate, it is possible that a typical ENT exam would find her TVF function to be WNL. However, the slowness of movements seen here is markedly

abnormal. It is also possible that the sluggishness of TVF abduction during expulsive cough efforts could obstruct airflow during cough efforts.

CHAPTER IV: DISCUSSION

This study is the first to examine cough-related TVF kinematic measures in individuals with MND. In addition, while it is well known that PECF declines in MND,^{12,75,76} this study also reports additional cough-related airflow measures, i.e., EPRT and VA, for individuals with MND. Mahajan and colleagues have reported that peak velocity time during cough, which by definition is the same as EPRT in this study, is determined by the laryngeal opening at the onset of cough.⁷⁷ However, this assumption has not previously been verified by direct laryngeal endoscopy. This topic was explored in this study and is discussed in detail in the “associations between TVF kinematics and cough-related airflow” section below. This study provided evidence of impairments across both airflow measures and TVF kinematics during the expulsion phase of cough in MND. In addition, the adequacy of laryngeal and supraglottic closure during the compression phase of cough was examined. Specific research questions are discussed in the context of prior literature below.

Another important purpose of this research was to evaluate the laryngeal contribution to volitional cough dysfunction in bulbar MND. This study is the first to evaluate the relationship between the extent and speed of TVF movements during the cough sequence and simultaneously measured cough-related airflow measures. The results of this study provide preliminary evidence to suggest a potential relationship between measures of TVF kinematics and cough-related airflow in individuals with MND.

Simultaneous laryngeal endoscopy and airflow measures have been collected in prior studies of phonation and vocal fold obstruction during exercise.^{73,84-87} In this study, the simultaneous measurement procedures were well tolerated across participants, except for instances of gagging with two MND subjects.

Cough-related airflow

Regarding cough-related airflow, this study examined the following question: “*Are there group differences between cough-related airflow measures, including PEF, EPRT and VA?*” While many prior studies have reported reduced PEF associated with MND,^{11,72,73} no other studies have been identified that examine the additional cough-related airflow measures of EPRT and VA in the MND population. In this study, PEF was reduced for the MND group. This was not surprising, as this has been reported in multiple studies previously.^{11,72,73} However, the EPRT was significantly larger and the VA significantly smaller in the MND group. It is well accepted that generation of a high peak airflow is important for cough effectiveness. However, the *timing* of the peak airflow, i.e., EPRT, may also be clinically significant.

Smith-Hammond and colleagues assert that EPRT and VA might be more sensitive to detecting risk for aspiration than subjective observations of reflexive cough associated with eating.^{4,88} This rationale is in part based on the fact that silent aspiration, i.e., aspiration without cough, can occur for some people with neurologic impairments. In studying volitional coughs produced by stroke survivors, EPRT and VA were independently associated with aspiration.⁴ EPRT during volitional cough was reported to have 91% sensitivity and 88% specificity in detecting aspiration in stroke survivors.⁸⁸ Volitional cough VA was reported to have 91% sensitivity and 92% specificity in detecting aspiration in the same population.⁸⁸ While norms on these measures do not currently exist, Smith-Hammond and colleagues, reported that an EPRT of >67 ms or a VA of <33 mL/s/s identified >90% of aspirators. Although Smith-Hammond and colleagues report an association between impaired volitional cough measures and aspiration,⁸⁸ they did not report observations on clinical outcomes, e.g., the development of aspiration pneumonia. Pitts and colleagues also reported correlations between EPRT and VA and aspiration as measured via videofluoroscopic swallow studies in individuals with Parkinson’s disease.⁸ They concluded that volitional cough ability may be associated with the degree of

airway protection.⁸ It is unclear if similar findings will be observed in individuals with MND. Future research will be needed to determine associations between cough-related airflow measures, such as EPRT, with other clinical factors, such as airway protection and/or laryngeal function.

TVF kinematics during cough

Regarding TVF kinematics during cough, several questions were addressed in this study: *1) Are there group differences between measures of maximum TVF abduction during the pre-compression inspiration and post-compression expulsion phases of cough? 2) Are there group differences in average TVF velocity during the pre-compression inspiration and post-compression expulsion phases of cough? and 3) Are there group differences in the pattern of TVF and supraglottic closure during compression phase of cough?* This study is the first to directly examine TVF kinematics during cough in individuals with MND. No significant group differences with pre-compression maximum TVF angle or pre-compression adduction velocity during the inspiratory phase of cough were observed. However, group comparisons during the expulsion phase of cough revealed reduced speed and extent of post-compression TVF abduction in the MND group. It can be argued that impairments of speed and extent of TVF movements may be more apparent in the expulsion phase of cough, as opposed to the inspiration phase, as TVF movements during expulsion phase are faster. Britton and colleagues reported that the expulsion phase post-compression TVF abduction velocity was much faster and more variable than the inspiratory phase pre-compression adduction, and much faster than similar gestures that occur in the context of speech.⁴⁰ The higher post-compression TVF abduction velocity seen in normally functioning individuals is also consistent with physiological observations reported by Hillel of an overlap of intrinsic laryngeal muscle adductors and abductors a few milliseconds before expulsion, effectively “spring loading” the

laryngeal abduction to quickly occur at the moment the intrinsic adductor muscles relax.⁴² Thus, coordination of post-compression TVF abduction requires a high degree of muscle coordination and speed and it is therefore more prone to dysfunction in the context of progressive muscle weakness associated with MND.

The pattern of TVF and supraglottic closure during the compression phase of cough observed in 100% of the control participants and 10/12 of the MND participants is the same as that previously reported by Britton and colleagues for healthy young individuals.⁴⁰ Britton and colleagues reported a consistent pattern of supraglottic closure characterized by extreme anterior-posterior compression (i.e., arytenoids in contact with the petiole of the epiglottis) and medialization of the FVFs, creating a sphincter-like airway closure.⁴⁰ Supraglottic closure is important to reinforce TVF airway closure and to prevent air escape during the compression phase of cough. Innervation for supraglottic structures via the superior laryngeal nerve is distinct from most of the intrinsic laryngeal muscles, which are innervated via the recurrent laryngeal nerve.⁸⁹ All of the participants in the current study demonstrated complete TVF closure. Therefore, dystussia or cough ineffectiveness in the MND group was not related to inadequacy of TVF closure. While 2/12 of the MND participants demonstrated inadequate supraglottic closure, other participants with cough ineffectiveness demonstrated adequate supraglottic closure. In addition, one of the participants with inadequate supraglottic closure during compression phase of cough demonstrated a PECF that was well within normal limits (see Case #1 above). Prior studies have revealed that volitional cough can remain relatively effective when the larynx has been bypassed altogether.⁴¹ Given these observations, adequacy of TVF or supraglottic closure may not be as important as TVF abduction facilitation of airway patency to cough effectiveness.

Associations between TVF kinematics and cough-related airflow

In order to examine associations between TVF kinematics and cough-related airflow during the expulsion phase of cough, the following research questions were addressed. *After controlling for variables known to effect cough effectiveness including respiratory muscle strength, 1) Is the maximum post-compression TVF abduction angle associated with PECF? And 2) Is the post-compression TVF abduction angular velocity associated with EPRT?* The variables of maximum post-compression TVF abduction angle and post-compression TVF abduction angular velocity were strongly associated with PECF and EPRT, respectively, when data were analyzed for MND and control participants combined. However, as indicated above, this most likely represents artifact owing to the distribution of variables in each group. The correlation between post-compression maximum TVF abduction angle and PECF approached statistical significance and demonstrated a strong positive relationship in the MND group. A moderately-strong negative relationship was observed in the correlation between EPRT and average TVF abduction velocity in both groups, but both were statistically non-significant. Further research with a larger number of participants will be needed to more definitively confirm or refute the associations between TVF kinematics and cough-related airflow.

It is important to consider whether or not cough-related airflow measures, such as EPRT, reflect TVF dysfunction. EPRT has been used for this purpose in prior research. For instance, "Tussometry" is a method of inferring vocal fold function from airflow data collected during voluntary cough.⁹⁰ In tussometry, one measure derived from airflow data is used: "peak value time" (PVT). PVT is the time (in milliseconds) from the onset of the cough expulsion to the peak airflow (in L/min). In a study comparing TVF function in people with unilateral recurrent laryngeal nerve paralysis to a control group, PVT was reported to be significantly increased in the group with unilateral recurrent laryngeal nerve paralysis despite no significant changes in peak cough flow.⁹⁰ PVT is essentially the same measure reported in this study and by Smith-

Hammond and colleagues under a different name, i.e., cough "expulsion or expiratory phase rise time" (EPRT).⁴ While this measure, PVT or EPRT, has demonstrated ability to distinguish participants with TVF dysfunction, there is no evidence to date that suggest that it can detect or differentiate between various types of vocal fold impairments and there have been no prior studies that measure EPRT during cough simultaneous with laryngeal endoscopy video imaging. Research comparing EPRT (i.e., PVT) between males and females revealed that females demonstrate a longer EPRT than males.⁹¹ It has been suggested that the longer EPRT seen with females may be attributable to the differences in the size of the larynx between the sexes.^{91,92} In this study, there were fewer females in the MND group compared with the control group; therefore, the longer EPRT previously reported for females would not explain the significantly longer EPRTs seen in the MND group in this study.

Analyses for a potential association between post-compression TVF velocity and EPRT were mixed in this study, in part due to the small number of research participants. However, since the MND group demonstrated significantly higher EPRT and significantly slower post-compression TVF velocity, it is estimated that the slower EPRT may reflect inadequate timing, extent and/or coordination of laryngeal abduction during cough. Determining efficient measures that reflect laryngeal slowness or incoordination may be of benefit clinically, e.g., for patients like those described in cases #1 and #2 above. However, Mahajan and colleagues point out that EPRT may also reflect PECF and/or lung volume, in addition to laryngeal function.⁷⁷ Further research examining associations between EPRT and laryngeal function, as well as implications of changes in EPRT is needed. In this study, the relative contribution of laryngeal versus respiratory musculature to slowness of the EPRT is unclear.

Other laryngeal observations

Otolaryngology observations were largely consistent with reports of laryngeal dysfunction associated with MND in prior literature, e.g., incomplete adduction, bowing, hyperfunction, and reduced abduction.¹⁷ However, “quivering” of the arytenoids and/or TVFs has not been previously reported. In this study, quivering of the arytenoids and/or TVFs was observed in 8/12 MND subjects. It was not observed in any of the control subjects. It was also not observed in any subjects with PLS. The quivering observed on the arytenoids and TVFs in 8/9 participants with ALS might reflect fasciculations of the arytenoids or TVF muscles. However, examination via electromyography would be needed to confirm the presence of fasciculations. It is also possible that quivering of the arytenoids or TVFs in participants with ALS might contribute to the perceptual vocal quality of “flutter,” i.e., rapid oscillation tremor, reported in prior literature, e.g., Buder & Strand.⁶¹

Cough phase durations

Mean durations of the phases of cough were slightly smaller in the MND group. However, no significant group differences were observed for cough phase durations. Duration of the phases of cough was variable in both the control and MND groups. The mean duration for inspiration was higher than the 0.65 seconds reported by Pitts & Bolser.⁹³ Duration of glottal closure during compression phase has been variable ranging from 0.04 to over 1 second.⁹⁴ The duration of glottic closure is thought to be related to the effectiveness of the compressive phase of cough.⁹⁴ Others have reported the duration of glottis closure to be approximately 0.2 s.³⁷ In this study the mean duration of the compression phase of cough, as measured via airflow was 0.35 s for controls and 0.32 s for MND group. Duration of the expulsion phase of cough has been reported to last approximately 0.03 to 0.05 s for the initial turbulent phase of the cough

and approximately 0.2 to 0.5 s for the prolonged lower flow portion of the expulsion.³⁷ The mean durations of expulsion phase of cough were longer for both control and MND groups in this study. This is most likely related to the task, as participants were instructed to cough as forcefully as possible.

Limits

This study has several limitations. First, the statistical analyses within and across groups were limited by relatively small numbers of participants, and it was not possible to adequately calculate number of participants to power this study due to a lack of prior research using the same variables. This study provides information on the outcomes that can be used in the calculation of power and sample size of future studies addressing this specific hypothesis.

Lung volume measures were not available for this study. It is possible that lung volume might have an effect on TVF kinematics and/or cough-related airflow data. Future research would benefit from analyses that control for lung volume.

Laryngeal endoscopy video imaging for this study was limited to 30 frames per second, and contained intermittent blurring and/or darker images. Research into cough-related TVF kinematics would benefit from high speed laryngeal endoscopy, improved resolution and development of methods for automatically tracking TVF movements.

The lack of normative data for the variables used in this study makes interpretation of data more challenging. Further research is needed to determine normative data for cough-related airflow measures and measures of TVF kinematics.

Finally, this is a cross-sectional study. It would be helpful to have longitudinal data in order to observe how participants change over time.

Clinical implications for rehabilitation sciences & future directions

The ability to cough is a key component of pulmonary defenses, and important to prevent complications related to dysphagia. Dysphagia is common in individuals with a variety of neurological impairments. Adequacy of pulmonary defenses is an essential consideration in the context of dysphagia assessment for rehabilitation patients. For individuals who are prone to aspiration, the ability to cough is an important means of guarding the lungs from the potential to develop infection, i.e., aspiration pneumonia. Dysphagia and dystussia frequently co-occur in individuals with neurological impairments.⁹⁵ This is true for the MND population, as both dystussia and dysphagia eventually occur for most diagnosed with MND. Dystussia is a condition that is common among many rehabilitation populations in addition to MND, e.g., spinal cord injury, stroke, traumatic brain injury, progressive forms of multiple sclerosis, and cerebral palsy. Research of associations between TVF kinematics and cough-related airflow has potential to pave the way for improved assessments of cough and laryngeal function, as well as development of improved interventions related to swallowing and cough across all of these groups.

In this study, most of the MND participants had impaired cough-related airflow measures of EPRT and VA, regardless of whether or not their PECF was adequate. Abnormally high EPRT measures may be indicative of laryngeal dysfunction or a degree of airflow obstruction during cough expulsion efforts. Abnormal EPRT and/or VA measures may also indicate a higher risk of aspiration.^{3,8} Further research will be needed to verify this in the MND population. This study, however, furthers our understanding of factors that may affect the ability to cough.

Reduced extent of TVF abduction was observed in some, but not all of the MND participants. However, even in the context of adequate TVF abduction, most with MND demonstrated impairments in the velocity and/or extent of TVF abduction during the initial post-compression portion of the cough expulsion phase. This relative slowness of TVF abduction

during the post-compression expulsion phase of cough most likely reflects laryngeal muscle flaccidity and/or spasticity due to MND and may contribute to dystussia. However, it is also possible that reduced lung volume and/or respiratory muscle impairments may affect the speed and extent of TVF abduction. Further research will be needed to examine these factors. For instance, examination of TVF kinematics during cough in individuals with spinal cord injury could help to determine if focal respiratory impairments have an impact on speed and extent of TVF movements. Further elucidation of these questions could have a large impact on assessment and intervention with rehabilitation populations.

Although statistical results pertaining to the associations between TVF kinematics and airflow were mixed, this study demonstrated that reductions in the extent and speed of TVF abduction during cough may contribute to dystussia. Contrary to the prior assumption by some that dystussia in individuals with bulbar impairments is related to inadequate TVF closure, the adequacy of TVF closure was not related to dystussia for the MND participants in this study. This observation is corroborated by prior literature indicating that TVF closure is not essential for an effective cough.^{37,41} While this study does not rule out the possibility of exacerbation of dystussia related to inadequate TVF closure, awareness of the potential for laryngeal dysfunction to obstruct airflow during the expulsion phase of cough expands clinical conceptualization of possible contributing factors to dystussia. This awareness could affect assessment and intervention procedures in the MND population.

In summary, this study has improved scientific understanding of normal and disordered TVF movement patterns during cough, and sought to elucidate associations between TVF kinematics and resulting airflow patterns during cough. Reductions in the speed and extent of TVF abduction are seen during expulsion phase of cough in individuals with MND. This may contribute to cough impairment and morbidity. Laryngeal involvement in MND may contribute to dystussia. This knowledge provides a basis for future research examining associations

between TVF kinematics and cough-related airflow. In order to more definitively determine the effect of laryngeal function on dystussia, associations between TVF kinematics in individuals with laryngeal dysfunction only should be examined. It would also be important to determine whether or not TVF kinematics are affected by respiratory muscle dysfunction in the context of normal laryngeal function.

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