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ORIGINAL ARTICLE

Associations Between Laryngeal and Cough Dysfunction in Motor Neuron Disease with Bulbar Involvement

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Abstract True vocal fold (TVF) dysfunction may lead to cough ineffectiveness. In individuals with motor neuron disease (MND), cough impairment in the context of dysphagia increases risk for aspiration and respiratory failure. This study characterizes differences and associations between TVF kinematics and airflow during cough in individuals with bulbar MND. Sequential glottal angles associated with TVF movements during volitional cough were analyzed from laryngeal video endoscopy examinations of adults with bulbar MND ($n = 12$) and healthy controls ($n = 12$) and compared with simultaneously collected cough-related airflow measures. Significant group differences were observed with airflow and TVF measures: volume acceleration ($p \leq 0.001$) and post-compression abduction TVF angle average velocity ($p = 0.002$) were lower and expiratory phase rise time ($p = 0.001$) was higher in the MND group. Reductions in maximum TVF angle during post-compression abduction in the MND group approached significance ($p = 0.09$). All subjects demonstrated complete TVF and supraglottic closure during the compression phase of cough, except for incomplete supraglottic closure in 2/12 MND participants. A strong positive relationship between post-compression maximum TVF abduction angle and peak expiratory cough flow was observed in the MND group, though it was not statistically significant ($r = 0.55$; $p = 0.098$). Reductions in the speed and extent of TVF abduction are seen during the expulsion phase of cough in individuals with MND. This may contribute to cough impairment and morbidity.

Keywords Motor neuron disease (MND) · Cough · Laryngeal function · True vocal folds (TVFs) · Amyotrophic lateral sclerosis (ALS) · Primary lateral sclerosis (PLS) · Deglutition · Deglutition disorders

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Introduction

Dystussia, the inability to cough effectively, is related to risk for aspiration and respiratory failure in individuals with neuromuscular dysfunction [1–6]. Dysphagia, respiratory impairments, and dystussia are common in motor neuron diseases (MND) such as amyotrophic lateral sclerosis (ALS) and primary lateral sclerosis (PLS).

It is well known that dystussia can occur due to weakness of the inspiratory and/or expiratory respiratory muscles [7–9]. In particular, weakness of the abdominal muscles results in difficulty generating sufficient pressure for a forceful, effective cough [9–11]. However, dystussia also occurs in people with conditions that affect the speech and swallowing muscles, i.e., the bulbar musculature, even with normally functioning inspiratory and expiratory respiratory muscles [9, 10, 12–14]. Dystussia in this group may be affected by weakened true vocal folds (TVFs), leading to reduced coordination of muscular responses with airflow, reduced subglottic pressure, and difficulty maintaining upper-airway patency during cough attempts [15]. In fact, Sancho and colleagues [16] have reported bulbar dysfunction to be a predictor of ineffective coughing during a respiratory tract infection in individuals with ALS.

Although dystussia in people with bulbar involvement is not well understood, variable patterns of laryngeal dysfunction are common in individuals with bulbar ALS [17, 18], including laryngospasm, incomplete adduction, bowing, hyperfunction, and reduced abduction [18–20]. Approximately 30 % of those with bulbar ALS present with impaired TVF abduction and passive paradoxical movements of the TVFs late in the course of the disease [17]. Murakami and colleagues [21] have described atrophic fibers in the laryngeal musculature of people with ALS, with particularly severe neurologic changes in the major TVF abductor, the posterior cricoarytenoid.

TVF dysfunction can have an obstructive effect on airflow during breathing. For instance, flow plateaus and sawtooth-like flow oscillations suggestive of changes in upper-airway caliber have been reported in people with bulbar involvement neuromuscular disease, including ALS [22]. In addition, reduced airway patency may occur due to laryngospasm or paradoxical movements of the TVFs [20, 23].

Understanding TVF kinematics and adequacy of airway patency during cough has important clinical implications. For instance, respiratory intervention prolongs survival in individuals with spinal-onset ALS and those with mild bulbar involvement, but it is not as effective for those with moderate–severe bulbar involvement [24, 25]. Similarly, cough-related intervention aids secretion clearance, but it is also not as effective for those with moderate–severe bulbar involvement [8, 12]. TVF impairments may be compromising airway patency and therefore contributing to the ineffectiveness of these interventions for individuals with moderate–severe bulbar involvement. Because volitional cough requires rapid, highly coordinated, active abduction of the TVFs, cough-related airflow measures may reflect laryngeal impairments leading to reduced airway patency. However, to date, no studies have directly measured the relationships between TVF movements, cough-related airflow, and airway patency in bulbar MND. Improved understanding of the underlying causes of dystussia in individuals with bulbar involvement could result in development of improved assessment methods and interventions for this group. Therefore, the primary purpose of this research was to examine the laryngeal contribution to volitional cough dysfunction in MND. The secondary purpose was to examine group differences between TVF kinematic and airflow measures during volitional cough.

Materials and Methods

Approval for this study was granted by the University of Washington Institutional Review Board. 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 healthy controls during a volitional cough task. Table 1 lists the variables that were measured.

Participants included 12 individuals with MND (3 females, age range = 54–76; 9 males, age range = 45–71) and 12 healthy volunteers (6 females, age range = 41–68; 6 males, age range = 56–66). Descriptive characteristics of MND severity and onset are given in Table 2. Inclusion criteria for participants with MND were a diagnosis of definite or probable ALS or PLS by a neurologist per the revised El Escorial criteria for ALS [26] and criteria published by Pringle and colleagues [27] for PLS, and current involvement of bulbar musculature (determined by a rating of $\leq$11 on the bulbar subsection of the ALS Functional Rating Scale—Revised [28]). Exclusion criteria included a history of neurological, pulmonary, or laryngeal disease prior to onset of MND-related symptoms. All MND participants demonstrated functionally intact cognitive skills. One of the 12 MND subjects had a smoking history; the remaining 11 MND subjects were nonsmokers. Healthy volunteers within the same age range as the MND participants and without a history of neurological, swallowing, or breathing disorders or smoking were recruited from the university and local communities.

As part of the nasolaryngeal endoscopy examination, the participants' most patent nasal–pharyngeal cavity was decongested using 0.05 % Afrin® (oxymetazoline) solution administered via an atomizer. Lidocaine (4 % solution) was administered for some participants (8/12 controls and 1/12 MND) by request to alleviate sensitivity associated with passing the scope. Approximately 2–3 min later, the KayPentax flexible fiberoptic laryngoscope (VNL 1140 K) was introduced via the nares. Airflow was measured at the mouth via a Hans-Rudolph Model 3813 pneumotach (Hans Rudolph, Inc., Shawnee, KS) and ADInstruments FE141 spirometer (ADInstruments, Inc., Colorado Springs, CO), connected to an oral flange, which was placed in the participant's mouth; a nose clip occluded nasal airflow. Adequacy of the lip seal was visually assessed to ensure there were no air leaks. Flow-volume calibration was completed prior to testing. The spirometry signals were digitized at 2 kHz, displayed with Labchart7 (ADInstruments) and temporally aligned with audio/video signals from laryngeal endoscopy.

Table 1 Study variables

	Variable	Measurement units
Cough-related airflow	PECF	L/s
	EPRT	ms
	VA	L/s/s
TVF kinematics	Maximum pre- and post-compression TVF abduction angle (inspiration and 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

PECF peak expiratory cough flow, *EPRT* expiratory phase rise time, *VA* volume acceleration, *TVF* true vocal fold, *L/s* liters/second, *s* seconds, *L/s/s* liters/second/second

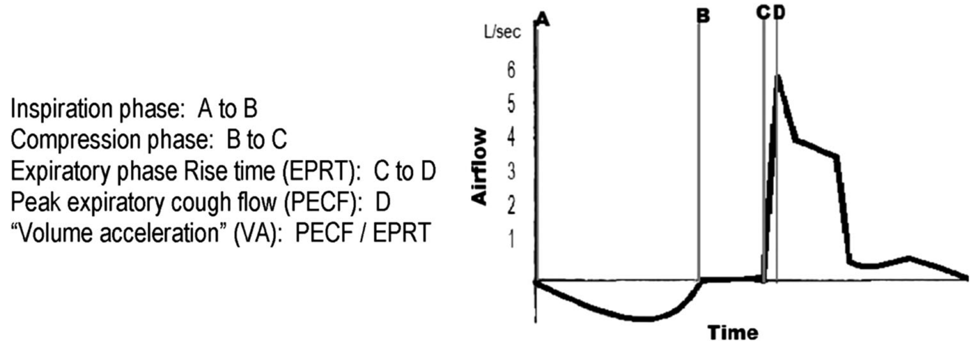
Participants were instructed to perform three volitional single cough maneuvers. During each task, airflow data and laryngeal endoscopy video of TVF movements were obtained simultaneously. Cough-related airflow measures (Table 1; Fig. 1) were obtained from the cough sample with the highest peak expiratory cough flow (PECF), except when visualization of the TVFs was inadequate (2/12 MND and 5/12 controls). In these instances, another cough sample with adequate visualization of the TVFs was analyzed. Laryngeal endoscopy data for two participants (1 MND and 1 control) were omitted due to inadequate visualization of the TVFs across all cough samples. One additional MND participant was omitted from expulsion phase analyses that required simultaneous measurement of airflow and spirometry measures due to inadequate visualization of the TVFs during the expulsion phase of cough when measured simultaneously with airflow. If the cough data contained a cough epoch, the first cough of the sequence was analyzed.

Table 2 Motor neuron disease (MND) participants

Diagnosis	Age	ALSFRS-R subscores (17)						
		Bulbar	Fine Motor	Gross Motor	Respiratory	Months after diagnosis	Months after ALS or PLS symptom onset	Location of first symptoms
Females								
ALS	59	6	1	5	9	8	25	Bulbar onset: tongue and speech
PLS	54	6	8	6	12	142	159	Spinal onset: legs
ALS	76	5	9	8	10	4	22	Bulbar onset: speech
Males								
ALS	71	9	6	6	3	32	Unknown	Spinal onset: hands and respiration
ALS	71	9	9	10	10	12	14	Spinal onset: right hand
PLS	53	8	8	6	9	25	63	Spinal onset: right foot drop
ALS	60	7	7	7	11	7	17	Mixed onset: speech and right thumb
PLS	59	8	9	6	8	133	205	Spinal onset: legs
ALS	45	7	1	3	11	12	21	Spinal onset: arms twitching
ALS	54	7	0	0	4	16	24	Spinal onset: right leg
ALS	63	2	12	11	11	7	10	Bulbar onset: speech
ALS	67	9	9	12	12	14	20	Mixed onset: Hand and speech

ALS amyotrophic lateral sclerosis, *PLS* primary lateral sclerosis, *ALSFRS-R* Amyotrophic lateral sclerosis functional rating scale—Revised

Fig. 1 Volitional cough-related airflow measures (from [27])



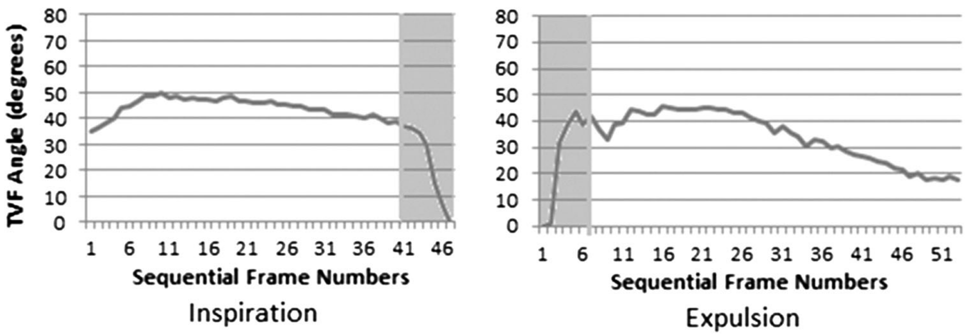


Fig. 2 TVF angle measures: regions of pre-compression adduction (inspiration phase) and post-compression abduction (expulsion phase) are highlighted in *gray*. The maximum true vocal fold (TVF) angle for pre-compression adduction was determined to be the maximum angle just prior to the pre-compression adduction. The maximum TVF angle for post-compression adduction was determined to be the maximum TVF angle within ± 0.15 s from the peak expiratory cough flow (PECF)

The measurement methods for sequential TVF angles during the inspiration and expulsion phases of cough were published by Britton and colleagues [29]. TVF angles were measured on 1,695 frames by the first author; 11 % of the frames were excluded due to inadequate visualization of the TVFs. The infraglottic aspect was marked as a surrogate of the TVFs on 2 % of the images where visualization of the TVFs was blocked by false vocal folds; marking of the infraglottic aspect slightly underestimated the TVF angle. The maximum TVF angle and average velocity to reach the maximum TVF angle were calculated within the *pre-compression adduction* and *post-compression abduction* regions (Fig. 2).

To examine inter-rater reliability, sequential and maximum TVF angle measurements were repeated by an experienced speech-language pathologist or otolaryngologist for 20 % of the participants (3 MND and 3 controls, randomly selected). To examine intrarater reliability, the first author repeated the TVF angle measurements for 20 % of the participants (3 MND and 3 controls, randomly selected), with more than 24 h between measurements. Reliability, in terms of absolute agreement for each frame, was analyzed with the use of two-way random model intraclass correlation coefficients (ICC) [30]. The inter-rater ICCs for 467 sequential angles and for 12 maximum glottal angles from 6 participants were 0.97 (95 % confidence interval [CI] = 0.96–0.98) and 0.99 (95 % CI = 0.95–0.99), respectively. The intrarater ICCs for 439 sequential angles and 12 maximum glottal angles measured from inspiration and expulsion phases of cough across 6 (3 controls and 3 MND) randomly selected participants were 0.99 (95 % CI = 0.98–0.99) and 0.99 (95 % CI = 0.99–1.0), respectively.

Nonparametric tests (Mann–Whitney *U*) were used to compare cough-related airflow and TVF kinematic variables by group. No adjustments were made in the significance level ($\alpha = 0.05$) for multiple comparisons due to the exploratory nature of this study. Associations between cough-related airflow and TVF measures were analyzed via Spearman rank correlation coefficients.

Results

Cough-Related Airflow

Statistically significant differences between MND and control groups were observed for two of the three cough-related airflow measures (Fig. 3). PECF ($p = 0.15$) and volume acceleration (VA) ($p < 0.001$) were reduced in the MND group. Expiratory phase rise time (EPRT)

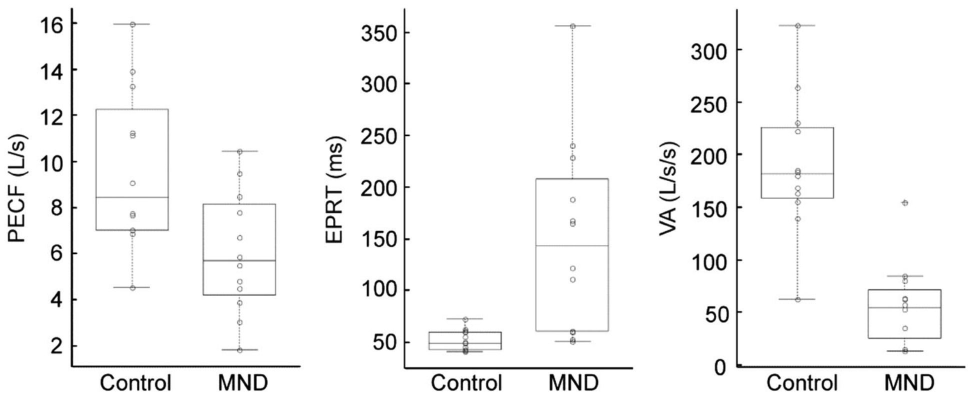


Fig. 3 Expulsion phase airflow measures: group comparisons. *Boxes* represent median and interquartile range. Whiskers extend to the lowest and highest data values within 1.5 times the interquartile range from the box edges. Any values located further than 1.5 times the interquartile range past box edges are indicated by asterisks. *Circles* indicate individual data points. Peak expiratory cough flow (PECF) measured in liters/second (L/s); expiratory phase rise time (EPRT) measured in milliseconds (ms), volume acceleration (VA) measured in liters per second per second (L/s/s)

($p = 0.001$) was larger and appeared more variable in the MND group.

TVF Kinematics

Forty-four video clips were analyzed. Maximum TVF abduction angle and the TVF angle average velocity for pre-compression adduction were analyzed for 11 MND participants (3 females) and 11 controls (6 females). The post-compression maximum TVF angle and the TVF angle average velocity for post-compression abduction were calculated for 10 MND participants (3 females) and 11 controls (6 females). Group differences for the post-compression maximum TVF angle approached significance ($p = 0.09$), with the MND group demonstrating smaller and more variable maximum TVF angles (Fig. 4). Group differences for the post-compression abduction TVF angle average velocity were statistically significant, with the MND group demonstrating slower and more variable TVF angle average velocity ($p = 0.002$) (Fig. 4). No statistically significant differences were observed between the groups with respect to the maximum pre-compression TVF angle or the pre-compression adduction TVF angle average velocity. Thus, the maximum TVF angle and average TVF velocity were reduced for the MND group during the expulsion phase of cough only. All of the MND and control participants had complete TVF closure during the compression phase of cough. Supraglottic closure was complete in all participants except two of the MND participants.

Associations Between Cough-related Airflow and TVF Kinematics During Expulsion Phase of Cough

Analysis for associations between cough-related airflow and TVF kinematic measures was completed for 10 MND participants (7 males) and 11 controls (5 males). MND participants demonstrated a strong positive correlation between PECF and maximum TVF angle that approached statistical significance ($r_s = 0.55$; $p = 0.098$). Control participants showed a small linear correlation between PECF and maximum TVF angle with $r_s = 0.082$ ($p = 0.81$). Fig. 5 displays a scatterplot illustrating the relationship between PECF and maximum post-compression TVF angle for both groups.

A moderately strong negative relationship between EPRT and the TVF abduction average velocity was seen for MND participants ($r_s = -0.503$; $p = 0.14$) and controls ($r_s = -0.209$; $p = 0.54$); however, neither were statistically significant. Fig. 6 displays a scatterplot illustrating the association between EPRT and TVF abduction average velocity for both groups.

Descriptive Group Comparisons

FVC, in terms of the percentage of the predicted normal values for participants [31], and MIP/MEP measures are presented in order to provide descriptive statistics pertaining to the participant's pulmonary function status. The highest of three trials was analyzed for all participants. As expected, the MND group had lower FVC than controls ($p \leq 0.001$). Four of the MND participants had difficulty with lip seal during the MEP measures. In these instances, manual assistance was provided to help with the adequacy of closure of the lips. As expected, MIP and MEP measures were lower in the MND group ($p = 0.001$).

The duration of each phase of cough was derived from airflow data for all participants. Group comparisons were not statistically significant: inspiration phase duration, $p = 0.12$; compression phase duration, $p = 0.69$; and expulsion phase duration, $p = 0.42$. Fig. 7 shows the

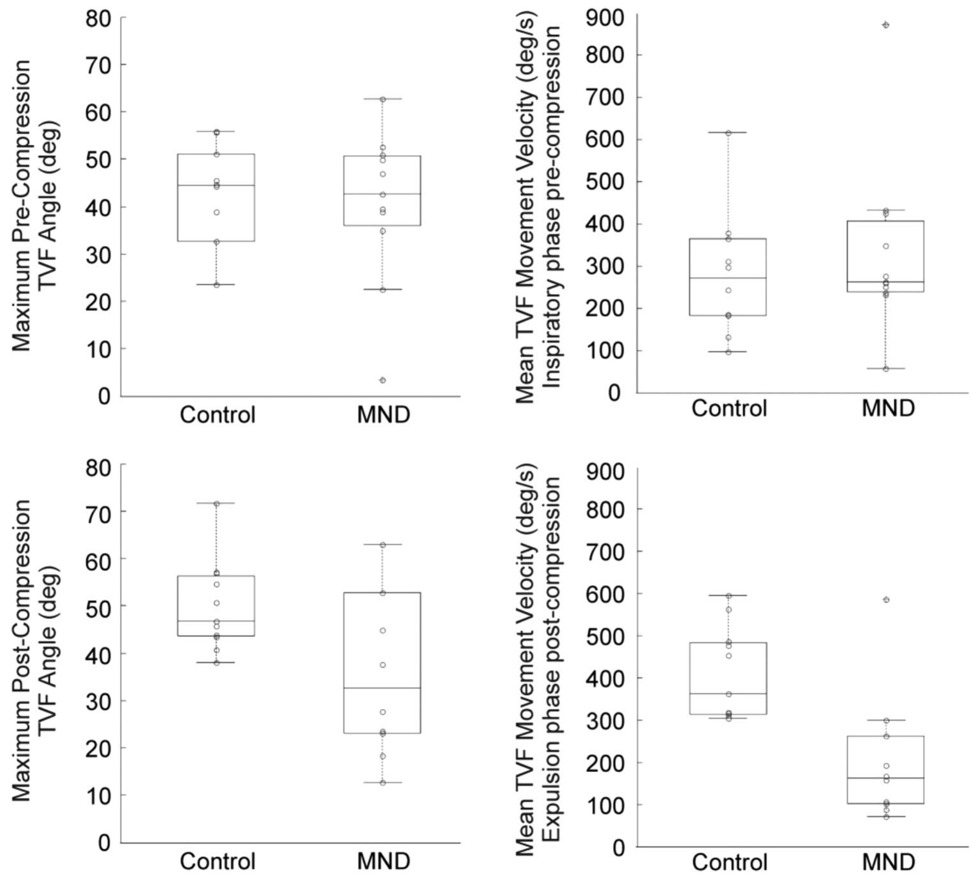


Fig. 4 Maximum TVF angles (*left side*) and TVF angle average velocity (*right side*): group comparisons. Maximum true vocal fold (TVF) angle or pre-compression adduction = maximum angle just prior to the pre-compression adduction. Maximum TVF angle for post-compression abduction = maximum TVF angle within ± 0.15 s from the peak expiratory cough flow (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

durations for the controls and the MND group across each phase of cough.

Discussion

This study was the first to examine cough-related TVF kinematics in individuals with MND. In addition, while it is well known that PECF declines in MND [7, 32, 33], this study reported additional cough-related airflow measures, e.g., EPRT. Another important purpose of this research was to determine 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 and simultaneously measured cough-related airflow measures. The results of this study provide preliminary evidence to suggest a potential relationship between TVF kinematics and cough-related airflow in individuals with MND. Understanding this relationship may help with assessment and intervention in this population.

Cough-Related Airflow

As expected, PECF was reduced for most in the MND group. However, EPRT was significantly larger and VA significantly smaller in the MND group (Fig. 3). It is well accepted that generation of high peak airflow is important for cough effectiveness. However, the *timing* of the peak airflow, e.g., EPRT, may also be clinically significant. Smith-Hammond and colleagues [2, 34] assert that EPRT and VA might be more sensitive for detecting risk for aspiration than subjective observations of reflexive cough associated with eating. EPRT and VA have previously been found to be associated with aspiration in individuals with stroke [2] and Parkinson's disease [6]. While norms do not currently exist, Smith-Hammond and colleagues [2] reported that an EPRT of >67 ms identified >90 % of aspirators in individuals after stroke. In the current study, 8/12 MND participants had an EPRT >67 ms. In addition, Sancho and colleagues [16] report reduced VA (called "PCF acceleration" in their study) to be a predictor of ineffective spontaneous cough during a respiratory tract infection.

TVF Kinematics During Cough

Group comparisons during the expulsion phase of cough revealed reduced speed and a trend toward reduced extent of post-compression TVF abduction in the MND group. It is possible that the laryngeal abductors may be more prone

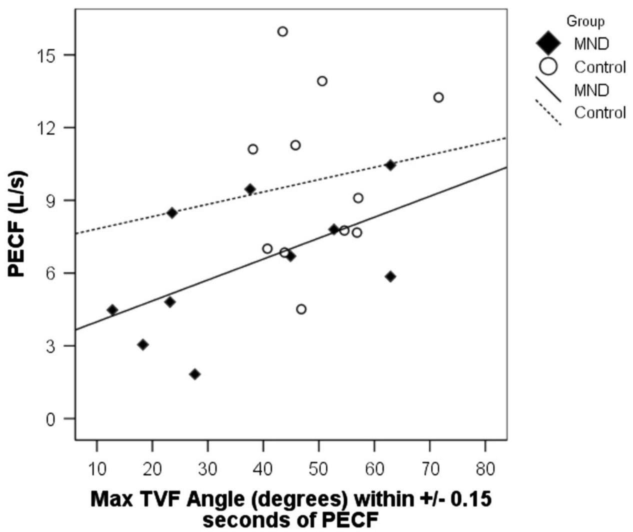


Fig. 5 Associations between PECF and maximum TVF angle

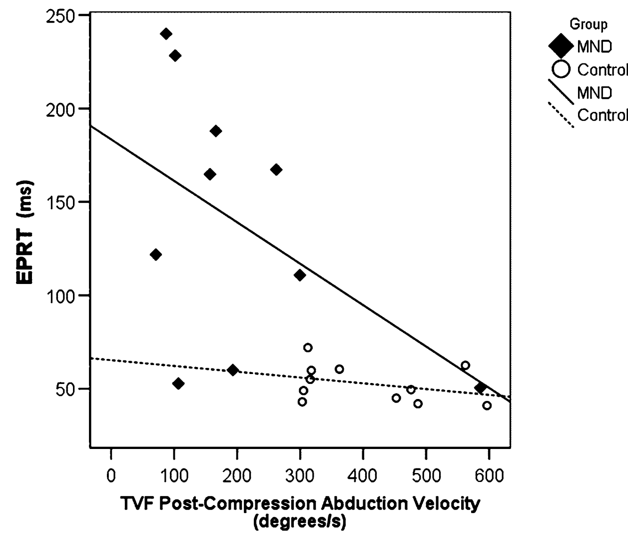


Fig. 6 Associations between EPRT and TVF post-compression abduction average velocity

to neurologic dysfunction in the individuals with ALS. There are more intrinsic laryngeal muscles for adduction than there are with abduction. In addition, Murakami and colleagues [21] report particularly severe atrophy in the muscle fibers of the posterior cricoarytenoid, the major TVF abductor muscle, in individuals with ALS. It can also be argued that impairments of speed and extent of TVF movements may be more apparent in the expulsion phase of cough than in the inspiration phase, as TVF movements during expulsion phase are faster. Britton and colleagues [29] report that for young healthy participants, 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. The higher post-compression TVF abduction velocity seen in normally functioning individuals is also consistent with the electromyographic observations by Hillel [35] 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. Thus, coordination of post-compression TVF abduction requires a high degree of muscle coordination and speed and it may therefore be more prone to dysfunction in the context of progressive muscle weakness and/or spasticity associated with MND.

The pattern of TVF and supraglottic closure during the compression phase of cough observed in all control participants and 10/12 of the MND participants was the same as that previously reported by Britton and colleagues [29] for healthy young individuals. All of the participants in the current study demonstrated complete TVF closure. Therefore, dystussia in the MND group was not related to inadequacy of TVF closure in this sample. 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 demonstrated a PECF that was well within a normal range. Prior studies have revealed that volitional cough can remain relatively effective when the larynx has been bypassed, such as by tracheostomy [36]. Given these observations, adequacy of TVF or supraglottic closure may not be as important as TVF abduction facilitation of airway patency to cough effectiveness. As indicated above, the relative slowness of TVF abduction during the post-compression expulsion phase of cough seen in the MND group may reflect degeneration of the major laryngeal abductor (posterior cricoarytenoid) and/or laryngeal muscle flaccidity and/or spasticity due to MND which disrupts the rapid, highly coordinated active TVF abduction needed for an effective cough. However, it is also possible that reduced lung volume, respiratory muscle impairments, and/or reflexively triggered cough may affect the speed and extent of TVF abduction. Further research is needed to examine these factors. Although statistical results pertaining to the associations between TVF kinematics and airflow were mixed, this study demonstrated that reductions in the speed and perhaps the extent of TVF abduction during cough may contribute to dystussia in MND.

Associations Between TVF Kinematics and Cough-Related Airflow

Findings for a potential association between post-compression TVF velocity and EPRT were mixed in this study,

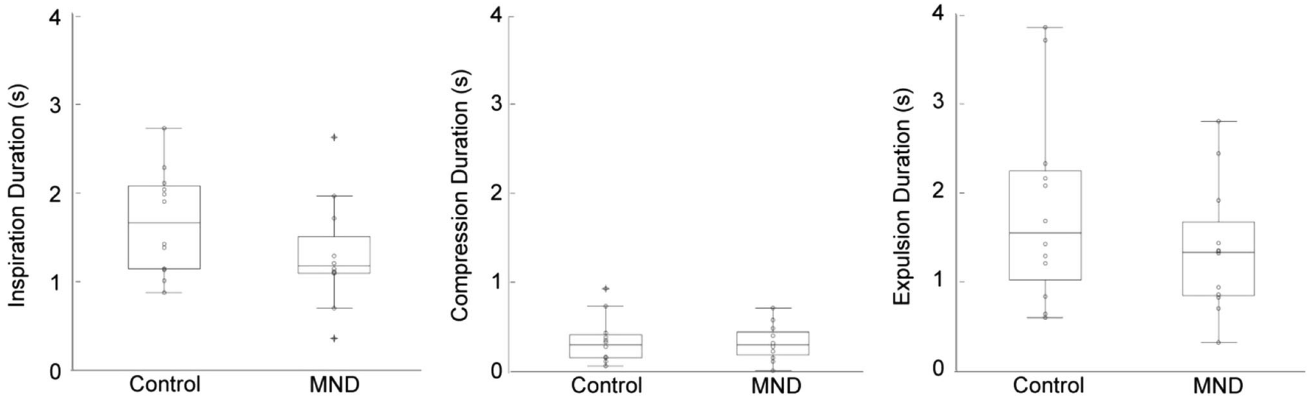


Fig. 7 Duration of the phases of cough: group comparisons. *Boxes* represent median and interquartile range. Whiskers extend to the lowest and highest data values within 1.5 times the interquartile range from the box edges. Any values located further than 1.5 times the interquartile range past box edges are indicated by *asterisks*. *Circles* indicate individual data points

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 and cost-effective measures that reflect laryngeal slowness or incoordination may be of benefit clinically. Other researchers have reported that EPRT (called "peak velocity time" in these prior studies) during cough is determined by the laryngeal opening at the onset of cough and therefore may reflect laryngeal function [37, 38]. However, Mahajan and colleagues [38] point out that EPRT may also be related to lung volume, in addition to laryngeal function. Suleman and colleagues [39] investigated the use of a mechanical glottis in individuals with MND and observed improvements in PECF and EPRT. Further research examining associations between EPRT and laryngeal function, as well as the implications of changes in EPRT, is needed. In this study, because all participants had mixed bulbar and spinal involvement, the relative contribution of laryngeal versus respiratory musculature to slowness of the EPRT is unclear.

Limitations

The current findings should be considered with the study's limitations in mind. The primary limitation is that a relatively small number of participants were included. In addition, none of the MND participants had purely bulbar involvement; all had at least some spinal involvement to varying degrees. Finally, lidocaine was used to anesthetize 8/12 controls and 1/12 MND participants prior to collection of endoscopy data. It is possible that use of lidocaine may alter laryngeal function and/or the cough response. Indeed, lidocaine is frequently used to inhibit the cough response in individuals suffering from chronic cough and/or coughing discomfort during procedures such as extubation [40, 41]. However, Mahajan and colleagues [42] report that use of lidocaine has had no measurable effect on laryngeal physiology during volitional coughing. It is very unlikely that the use of lidocaine had any measurable effect on data collection for several reasons: First, volitional (as opposed to spontaneous or reflexive) cough was studied. In theory, volitional cough should be much less affected by changes in sensation than reflexive cough. Second, lidocaine was administered to only one MND participant (vs. 8/12 controls). Therefore, the reduced extent and velocity of TVF abductor movements during the expulsion phase of cough in the MND group cannot be attributed to use of lidocaine. If there is any effect, it would have been to potentially diminish TVF function in the control group.

Conclusion

The ability to cough is a key component of pulmonary defenses and important to prevent complications related to dysphagia. This is relevant for the MND population, as both dystussia and dysphagia eventually occur for most individuals diagnosed with MND. This study has demonstrated the use of TVF kinematics measures to better understand how TVF weakness can affect cough efficiency and furthered our understanding of factors in the MND population that may affect the ability to cough. Reductions in the speed and extent of TVF abduction were seen during the 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 in which associations between TVF kinematics and cough-related airflow are examined. This research would have 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.

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Conflict of interest The authors have no conflicts of interest to declare.

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