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The Role of Vocal Fold Bowing on Cough and Swallowing Dysfunction in Progressive Supranuclear Palsy

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Objectives: Progressive supranuclear palsy (PSP) is a neurodegenerative disease which results in cough and swallowing dysfunction and aspiration pneumonia. Relationships among vocal fold atrophy, cough, and swallowing have been identified in related diseases, but remain unknown in PSP. This study examined: 1) the prevalence of vocal fold bowing in PSP, and 2) the influence of vocal fold bowing on cough and swallowing in PSP.

Study Design: Prospective Cohort Study.

Methods: Twenty-three participants with PSP completed instrumental assessments of cough and swallowing. Vocal fold bowing (BI) and swallowing safety (PAS) was assessed using flexible laryngoscopy. Measures of cough effectiveness were obtained using spirometry. Statistical analyses were used to determine the frequency of mild–moderate (BI > 0) and severe (BI > 12.2) bowing, and to assess the influence of BI on PAS and cough effectiveness in PSP.

Results: Fifty-two percent (n = 12) of participants exhibited severe bowing while 48% (n = 11) exhibited mild-to-moderate bowing. Voluntary cough peak expiratory flow rate ($P = .01$), as well as reflex ($P = .02$) and voluntary ($P = .005$) cough volume acceleration were lower for participants with severe BI when compared to mild-to-moderate BI. However, BI did not influence PAS ($P > .05$).

Conclusions: Findings from this study suggest that vocal fold bowing is highly prevalent in PSP and associated with reduced reflex and voluntary cough effectiveness. These findings provide insight into the pathophysiology of compromised airway protection in this patient population. Future studies should examine vocal fold atrophy as a treatment target for behavioral and medical intervention in PSP.

Key Words: Progressive supranuclear palsy, aspiration, cough, vocal fold atrophy, bowing index, laryngoscopy..

Level of Evidence: 3 (Prospective Observational Study)

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INTRODUCTION

Progressive supranuclear palsy (PSP) is the most common form of atypical parkinsonism, neuropathologically classified as a tauopathy, a family of disease characterized by neuronal loss, gliosis and accumulation of tau protein in involved areas.[1,2] Frequent pathologic changes and neural degeneration within the basal ganglia and brainstem result in symmetric parkinsonism (bradykinesia, rigidity, tremor, and postural instability) as well as vertical gaze palsy and behavioral disturbances.[2] Neuropathological changes also negatively influence bulbar functions and therefore result in a high prevalence of airway protective disorders including swallowing and cough dysfunction.[3] Concomitant impairments in these airway protective behaviors (ie, cough and swallowing) contribute to the development of aspiration pneumonia—a leading cause of death in PSP.[4]

Swallowing dysfunction is highly prevalent in PSP. Research involving objective methods of swallowing function in people with PSP have identified dysphagia to be frequently characterized by reduced lingual and masticatory movements, incomplete oral bolus control, delayed pharyngeal swallow, reduced upper esophageal sphincter relaxation, esophageal dysmotility, pharyngeal residue, and aspiration.[3,5–8] While no studies have objectively evaluated cough in this patient population, both an absent cough response and reduced reflex cough effectiveness have been subjectively described in PSP.[8]

Swallowing and cough are highly skilled sensorimotor behaviors that require multiple anatomic and physiologic mechanisms for effective and efficient functioning. Specifically, the vocal folds play a critical role in airway protection during the swallow by adducting together to

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Authorship N.E., J.A.C., and M.S.T. conceived and designed the study; N.E., J.A.C., J.C.B., and J.S.S. collected the data; N.E., J.A.C., and J.C.B. analyzed and interpreted the data; N.E., J.C.B., J.A.C., J.S.S., N.V., and M.S.T. prepared the manuscript; and M.S.T. and N.V. supervised the findings of this work. All authors discussed the results and contributed to the final manuscript.

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seal off the lower airway and prevent pulmonary aspiration of ingested foods and liquids. Additionally, complete vocal fold adduction and glottic closure during the compressive phase of cough facilitates generation of subglottic pressure required for forceful and efficient expiratory cough airflow. In Parkinson's disease (PD), vocal fold atrophy is a common laryngeal abnormality[9,10] and recent work by our group has identified that changes in this laryngeal structure were associated with impaired swallowing safety and aspiration in people with PD. This suggests that vocal fold atrophy may be a clinically significant finding related to airway protection in other Parkinsonian syndromes as well.[11]

No studies have examined the presence of vocal fold bowing in PSP. Furthermore, the influence of vocal fold bowing on airway protection in persons with PSP remains unknown. Understanding the relationship between laryngeal dysfunction and airway protective deficits in PSP would facilitate the development of behavioral and medical interventions to improve health outcomes. Therefore, the aims of this study were to: 1) describe the prevalence of vocal fold bowing in PSP as a function of sex, age, and disease duration, and 2) investigate the relationship between vocal fold bowing, cough function, and swallowing safety. We hypothesized that vocal fold bowing would be a common pathologic finding in this population, and would increase as a function of age and disease duration. We also hypothesized that worsening vocal fold bowing would be associated with worsening impairments in cough and swallowing function.

METHODS

Participants

This study is a secondary analysis of a larger prospective study examining cough and swallowing in people with PSP. Participants were prospectively recruited to a clinical research laboratory between 2017 and 2019. Participants with suggestive, possible, or probable PSP, as diagnosed by a movement disorders neurologist, were included. Diagnoses were determined based on the movement disorder society clinical diagnostic criteria for PSP.[12] Exclusion criteria included 1) other neurological disorders or insult (eg, stroke, brain tumor), 2) history of head and neck cancer, 3) respiratory disease (eg, chronic obstructive pulmonary disease, asthma), 4) smoking in the last 5 years, or 5) inability to tolerate a flexible laryngoscopic procedure. Demographic information was collected from all participants including age, sex, and disease duration. This study was approved by the Columbia University institutional review board (IRB #: 17-396) and was conducted in accordance with the Declaration of Helsinki. All participants provided informed consent prior to study participation.

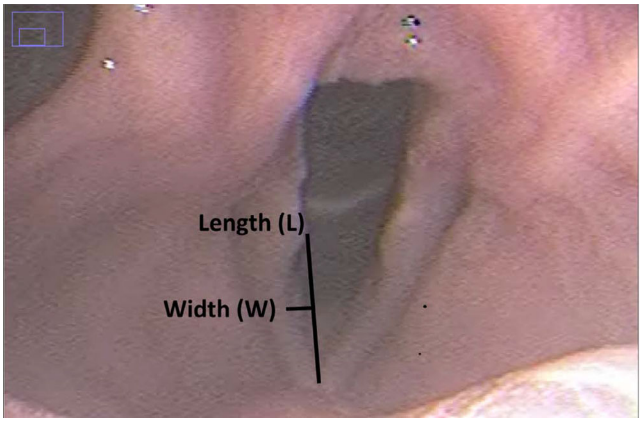

Fig 1 Bowing index methodology. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

Study Design

Once enrolled, participants completed same-day assessments of laryngoscopy, flexible endoscopic evaluation of swallowing (FEES), and spirometric reflex and voluntary cough testing.

Laryngoscopy

Laryngoscopic examinations were completed by a speech-language pathologist using a high resolution 3.0-mm diameter flexible distal chip laryngoscope (ENT-5000; Cogentix Medical, New York, USA). The laryngoscope was passed transnasally without the use of a topical anesthetic or vasoconstrictors and positioned with the tip of the scope within the mid-oropharynx in order to view the pharynx, larynx, and subglottic space. Laryngoscopic assessment included examination of laryngeal anatomy during tidal breathing.

Frame by frame analysis of videos was performed by two authors (N.E., J.A.C.) in QuickTime 7 (Apple, Cupertino, CA, USA) in order to capture images of the membranous vocal folds (ie, vocal process to anterior commissure) for each participant. Images were obtained during quiet tidal exhalation and were used for analysis if the entire length of both the left and right membranous vocal folds were simultaneously visualized. The still images were uploaded to ImageJ visual analysis software (National Institutes of Health, Bethesda, MD, USA) for quantitative measurement of vocal fold bowing using the normalized bowing index (BI). Measures of the BI were made by using the formula: $BI = W/L \times 100$, where "L" was the length of the vocal fold measured from the anterior commissure to the tip of the vocal process expressed in pixels and "W" was the maximum distance from "L" to the vocal fold edge at the mid-membranous area (Fig. 1).[13] This was completed for both the left and right vocal folds. Total BI was then calculated by summing together the left and right BI values.

All BI measures were completed by one primary rater, with a random 20% of images repeated for analysis by a secondary rater. Both raters were blinded to all other data, including participant identity, demographic information, and swallowing and cough function.

Flexible Endoscopic Evaluation of Swallowing (FEES)

Immediately following the laryngoscopic examination, a FEES was completed. During the FEES, participants completed self-administered trials of the following thin liquid boluses: 5 mL (1×), 10 mL (3×), 90 mL (3×), and 150 mL (1×). The tip of the endoscope was then advanced into the laryngeal vestibule to visualize residue patterns within the larynx and subglottic space. Trials were presented in a sequential order from smallest to largest volume. Criterion for bailout included gross aspiration in more than one trial without the ability to clear aspirate material (spontaneously or with clinician assistance) to a minimal or trace amount.

During the FEES, all boluses were thin liquid barium water. This was prepared by mixing three tablespoons (~24 g) of barium powder (E-Z-Paque Barium Sulfate for Suspension (96% w/w; E-Z-EM Canada, Inc.) diluted into a cup of 100 mL filtered tap water. Barium water was used since it has been found to have increased sensitivity for the detection of airway invasion compared to other colorants.[14] Viscosity testing was performed for all boluses using the International Dysphagia Diet Standardization Initiative (IDDSI) Flow Test methodology,[15] with all liquids demonstrating an IDDSI Level 0 (thin liquid viscosity level).

Swallowing safety was judged for the largest volume of liquid presented to the participant using the 8-point Penetration-Aspiration Scale (PAS).[16] The largest volume was used for analysis of swallowing safety since this has been shown to have the highest probability for identifying swallowing safety impairments.[17] PAS ratings were completed blindly by two expert speech pathologists (J.C.B., J.A.C.) with 20% of videos randomly selected for inter- and intra-rater reliability.

Cough Testing

Reflex and voluntary cough testing was completed with participants seated comfortably in an upright position. Participants were fitted with a cushion facemask covering the nose and mouth which was coupled to a t-connector, respiratory filter, pneumotachograph (MLT 1000, ADInstruments), differential transducer (Validyne MP45), and a side delivery port with a valve for nebulizer connection. Three trials of voluntary cough were elicited from participants by verbal instruction to "cough as if something went down the wrong pipe." Cough reflex testing was then completed using a DeVilbiss T-piece (DeVilbiss Healthcare) nebulizer connected to a dosimeter (Koko Dosimeter, nSpire Health) which was used to aerosolize solutions of capsaicin during a single tidal inhalation. Capsaicin was dissolved in a vehicle solution of 80% saline and 20% ethanol and prepared to four different concentrations: 0, 50, 100, and 200 μM. Each concentration was presented three times in a randomized block order. Participants were instructed to "breathe in and out of your mouth, and cough if you need to."

Cough airflow signals were digitized and recorded to a desktop computer via PowerLab Data Acquisition hardware for offline analysis using LabChart 8 (ADInstruments). Airflow measures for reflex and voluntary coughs were completed by a blinded research assistant and included peak expiratory flow rate (PEFR; Liters/second) and cough volume acceleration (CVA; L/s/s). For reflex cough, airflow measures were obtained from the first cough response following presentation of 200 μM capsaicin. For voluntary cough, airflow measures were also derived from the participant's first voluntary cough. Across both voluntary and reflex cough, airflow measures were obtained from the first cough epoch.

Statistical Analysis

Intra-class correlation coefficients were used to assess inter- and intra-rater reliability. ICCs ≥ 0.90 were considered "excellent", between 0.75 and 0.90 was "good", between 0.50 and 0.75 was "moderate", and < 0.50 was "poor. Weighted Cohen's kappa (κ) was used to examine inter- and intra-rater reliability of PAS ratings. Descriptive statistics including frequency count, means, and standard deviations were reported for all outcome measures. The frequency of "mild-to-moderate" (BI > 0) and "severe" (BI ≥ 12.2) vocal fold bowing was also recorded. A BI ≥ 12.2 represents one standard deviation above the mean for people with presbylarynges,[18] and was therefore used as a cut-off value for severe vocal fold bowing, all other scores below 12.2 and above 0 were considered mild-to-moderate. Hierarchical linear regressions were used to examine the relationships between BI and disease duration, age, and sex.

An ordinal logistic regression was performed to examine the relationship between BI and swallowing safety. Hierarchical linear regressions were used to examine the relationship between reflex and voluntary cough airflow outcomes and BI, while controlling for age, sex, and disease duration. ANCOVAs were performed to assess differences between groups across

TABLE I.
Demographic Characteristics and Laryngoscopic Findings.

Characteristic	Distribution
Age, mean in yrs (SD) [range]	72.39 (6.96) [54–85]
Sex, no. (%)	
Female	7 (30%)
Male	16 (70%)
Disease duration, mean in years (SD) [range]	5.03 (2.26) [1.88–10.88]
PAS score, no. (%)	
1	2 (9%)
2	0 (0%)
3	5 (22%)
4	2 (9%)
5	5 (22%)
6	0 (0%)
7	1 (4%)
8	8 (34%)
BI, mean (SD) [range]	13.63 (6.41) [3.41–23.29]

BI = Bowing Index; PAS = Penetration-Aspiration Scale; SD = standard deviation.

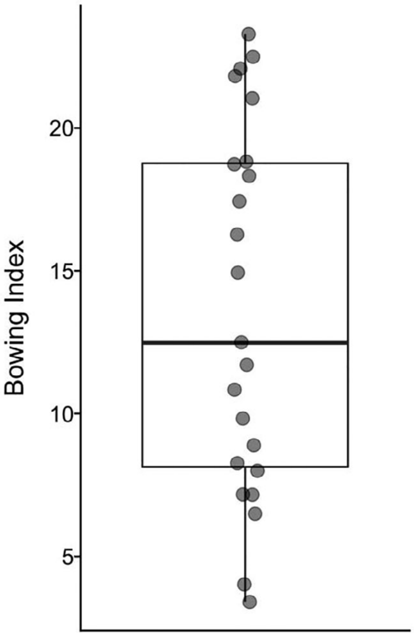

Fig 2 Distribution of vocal fold bowing.

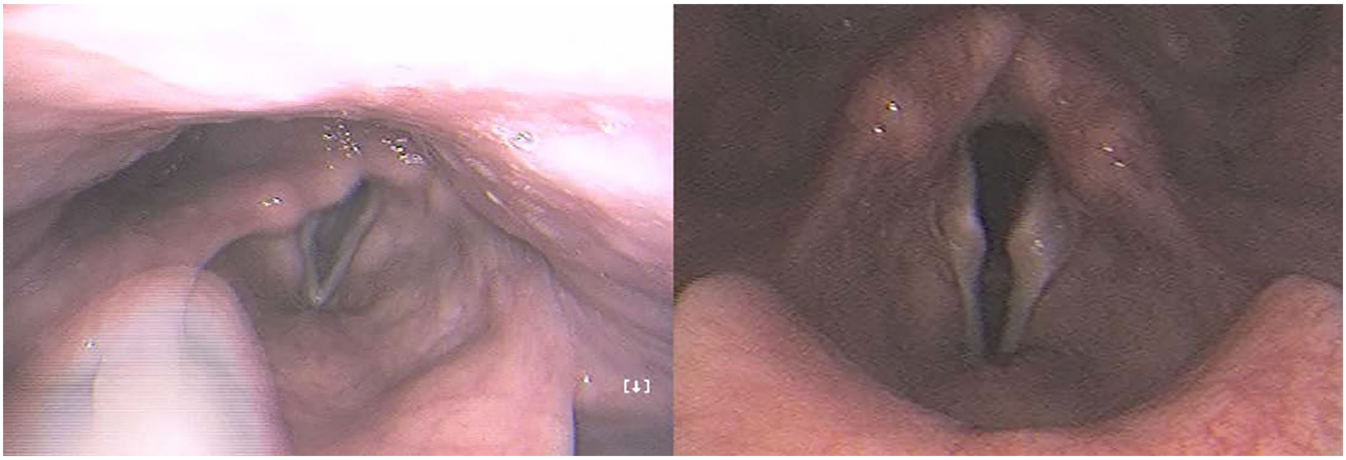

Fig 3 Example of mild-to-moderate vocal fold bowing (left; bowing index = 10.0) and severe vocal fold bowing (right; bowing index = 22.1). [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

TABLE II.
Comparison of Cough Airflow Outcomes between Participants with Mild-to-Moderate and Severe Vocal Fold Bowing.

Outcome	Estimate	SD	Test Statistic	Unadjusted *P* Value	Effect Size
Reflex PEFR			$F = 2.09$	.170	$\eta_p^2 = 0.13$
Mild-to-moderate BI	$M = 2.10$	0.42			
Severe BI	$M = 1.69$	0.69			
Reflex CVA			$F = 6.85$	.020*	$\eta_p^2 = 0.33$
Mild-to-moderate BI	$M = 46.65$	18.87			
Severe BI	$M = 24.19$	15.58			
Voluntary PEFR			$F = 9.22$	.010*	$\eta_p^2 = 0.44$
Mild-to-moderate BI	$M = 2.49$	1.89			
Severe BI	$M = 1.31$	0.40			
Voluntary CVA			$F = 11.61$	.005*	$\eta_p^2 = 0.49$
Mild-to-moderate BI	$M = 52.71$	31.80			
Severe BI	$M = 14.78$	14.17			

*$P < .05$ after Holm-Bonferroni adjustment.
BI = bowing index; CVA = cough volume acceleration; PEFR = peak expiratory flow rate; SD = standard deviation; η_p^2 = partial eta-squared.

cough outcomes while controlling for age and sex. A Kruskal Wallis test was also used to examine differences in PAS between these groups. Alpha was set at $P < .05$. Partial eta-squared (η_p^2) was used as a metric of effect size. A Holm-Bonferroni adjustment was used to control for multiple comparisons. Statistical analyses were performed in SPSS v 26.0.

RESULTS

Twenty-three participants (16 males, 7 females) with a mean age of 72.39 years (SD = 6.96) and disease duration of 5.03 years (SD = 2.62) met inclusion criteria (Table I). Inter-rater reliability of cough airflow measures was judged as "moderate" (ICC = 0.68). Inter- and intra-rater reliability of BI measures was considered "good" (ICC = 0.89) and "excellent" (ICC = 0.95), respectively. Absolute inter- and intra-rater agreement for PAS ratings was 80% (Cohen's $\kappa = 0.74$) and 100% (Cohen's $\kappa = 1.00$), respectively.

Laryngoscopic Findings

All participants demonstrated some degree of vocal fold bowing (BI > 0) with a mean BI of 13.60 (Fig. 2). Additionally, 12 participants demonstrated severe vocal fold bowing (*M* = 0.08, *SD* = 0.03), whereas 11 had mild-to-moderate vocal fold bowing (*M* = 0.19, *SD* = 0.03; Fig. 3). Age alone was not associated with BI when controlling for disease duration and sex (R^2 Change = 0.016, $P = .556$). Sex alone was not associated with BI when controlling for age and disease duration (R^2 Change = 0.055, $P = .274$). Disease duration alone was not associated with BI when controlling for age and sex (R^2 Change = 0.154, $P = .075$).

Swallowing Safety

Two participants demonstrated safe swallowing (PAS 1–2), 12 showed supraglottic penetration (PAS 3–5), and nine aspirated (PAS 6–8). Ordinal regression analysis revealed that BI was not associated with airway invasion (χ^2 = 123.66, P = .160). Given a lack of specific airway invasion events (PAS 2 and 6), a follow-up binary logistic regression was performed comparing BI between non-aspirators (PAS 1–5) and aspirators (PAS 6–8). Results showed no relationship between BI and aspiration controlling for age, sex, and disease duration (χ^2 = 3.70, P = .295, Nagelkerke R^2 = .210). Furthermore, there was no statistically significant difference in swallowing safety between participants with severe and mild-to-moderate BI (H = 1.17, P = .280).

Cough Function

Eighteen participants were able to complete reflex cough testing and 16 participants completed voluntary cough testing. No statistically significant relationships were found between BI and measures of reflex cough airflow, specifically PEFR (R^2 Change = 0.142, P = .158) and CVA (R^2 Change = 0.117, P = .175) when controlling for age, sex, and disease duration. There was no significant relationship between BI and measures of voluntary cough, specifically PEFR (R^2 Change = 0.185, P = .126) and CVA (R^2 Change = 0.213, P = .105) when controlling for age, sex, and disease duration. After a Holm-Bonferroni adjustment to correct for multiple comparisons, significantly decreased cough airflow was appreciated for participants with severe BI compared to mild-to-moderate BI across voluntary PEFR, voluntary CVA, and reflex CVA (Table II). No statistically significant differences in reflex PEFR were appreciated between groups (P > .05).

DISCUSSION

Cough and swallowing are important for preventing aspiration pneumonia—a leading cause of death in PSP. The vocal folds are important for safe swallowing and effective coughing, and are known to atrophy as an effect of aging and in neurodegenerative diseases such as PD. However, the prevalence of vocal fold bowing and its effect on cough and swallowing has not been previously evaluated in PSP. The present study investigated the prevalence of vocal fold bowing in PSP and the relationship between these anatomic changes, swallowing safety, and cough effectiveness.

All participants in this study demonstrated vocal fold bowing, with severe bowing present in over 50% of participants. Given the elevated age in our sample, the large prevalence of vocal fold bowing is unsurprising. Vocal fold atrophy develops in healthy adults as an effect of normal aging.[19] However, the incidence of vocal fold bowing in this study is higher than what would be expected of healthy individuals matched for age and sex.[20] Similarly, a high incidence of vocal fold bowing has been identified in Parkinson's disease, with a prevalence ranging from 70% to 94%.[9–11,21] Recent work by our group found 80% of people with PD exhibited some degree of bowing, with 20% demonstrating severe vocal fold bowing.[11] Interestingly, no relationship was found in this study between bowing index (BI) and age, sex, or disease duration alone when controlling for other variables. Nonetheless, the average BI in the present study was considered "severe" (13.63 ± 6.41) based on a prior study in an older, healthy cohort.[18] This is descriptively higher than what has been identified in young adults (3.6 ± 2.6), individuals with age-related vocal fold atrophy (6.8 ± 5.4), and individuals with PD (7.57 ± 5.06).[11,18]

The presence and severity of vocal fold bowing is likely a result of age and disease-specific changes in the peripheral and central nervous system. Loss of muscle mass and decreased or changed structure of the superficial lamina propria are the most common changes seen in age-related vocal fold atrophy.[19] In addition to changes in the laryngeal tissue, neurological and circulatory changes may also contribute to vocal fold atrophy. Particularly, a higher incidence of vocal fold atrophy has been identified in diseases affecting the nervous system.[10,22]

In PD, a relationship has been identified between vocal fold bowing and penetration/aspiration.[11] Because of this, we hypothesized a similar relationship to be present in PSP. However, our findings did not support this hypothesis. There are several potential reasons for these incongruent findings. First, methodological differences in BI were present between these two studies. In the present study, we captured maximal BI during rest breathing, often during tidal exhalation, whereas in the PD study BI was captured when the vocal folds were fully abducted.[11] Additionally, previous research examining swallowing safety in PSP has identified aspiration to predominately occur *before* the swallow.[8] In fact, aspiration in PSP is associated with delayed pharyngeal swallow initiation and reduced oral bolus control.[3, 6] This is in contrast to PD, where predictors of penetration/aspiration are associated with extent and timing of laryngeal vestibule closure.[23] Lastly, it is possible that this study was underpowered to detect differences in swallowing within this PSP cohort—most of whom had relatively severe bowing when compared to people with PD. Results may have differed if comparing people with severe bowing to people with no bowing.

Both voluntary and reflex cough effectiveness were associated with differences in BI in this PSP cohort. Reduced cough expiratory airflow was identified in participants with severe BI, as compared to those with mild-to-moderate BI. Given that complete vocal fold closure and subglottal pressure generation is required to produce an effective cough, these findings are unsurprising. However, it is interesting to note that these findings are in contrast to our group's recent findings in PD. It is unclear why cough effectiveness was not impacted by BI in the PD cohort but was in PSP. The rapid disease progression and increased vocal bowing in PSP, as compared to PD, may explain differences in findings. For example, people with PD may have developed compensatory strategies to accommodate for vocal fold bowing.

It should be noted that BI, which is used as a surrogate anatomical measure for vocal fold atrophy, may not be directly associated with vocal fold closure during cough and swallowing. While BI has been correlated with glottal gap during adduction[13] and remains a representative measure of vocal fold atrophy, future studies may consider examining the relationship between glottal gap during a breath-hold task and cough and swallowing. Additionally, future studies should continue to examine the relationships between laryngeal dysfunction and airway protective deficits in PSP, and consider vocal fold atrophy as a possible target for behavioral and medical intervention.

CONCLUSION

Vocal fold bowing is prevalent in people with PSP and appear to contribute to deficits in airway protection in this patient population. Therefore, clinician should attend to abnormalities in vocal fold bowing/atrophy when performing flexible laryngoscopy in people with PSP, and if severe, consider the potential for the patient to be at risk of impaired cough and swallowing function.

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