Decreased Cough Sensitivity and Aspiration in Parkinson Disease

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BACKGROUND: Aspiration pneumonia is a leading cause of death in people with Parkinson disease (PD). The pathogenesis of these infections is largely attributed to the presence of dysphagia with silent aspiration or aspiration without an appropriate cough response. The goal of this study was to test reflex cough thresholds and associated urge-to-cough (UTC) ratings in participants with PD with and without dysphagia.

METHODS: Twenty participants with PD were recruited for this study. They completed a capsaicin challenge with three randomized blocks of 0, 50, 100, and 200 μ M capsaicin and rated their UTC by modified Borg scale. The concentration of capsaicin that elicited a two-cough response, total number of coughs, and sensitivity of the participant to the cough stimulus (UTC) were measured. The dysphagia severity of participants with PD was identified with the penetration-aspiration scale.

RESULTS: Most participants with PD did not have a consistent two-cough response to 200 μ M capsaicin. UTC ratings and total number of coughs produced at 200 μ M capsaicin were significantly influenced by dysphagia severity but not by general PD severity, age, or disease duration. Increasing levels of dysphagia severity resulted in significantly blunted cough sensitivity (UTC).

CONCLUSIONS: UTC ratings may be important in understanding the mechanism underlying morbidity related to aspiration pneumonia in people with PD and dysphagia. Further understanding of decreased UTC in people with PD and dysphagia will be essential for the development of strategies and treatments to address airway protection deficits in this population.

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ABBREVIATIONS: Cr2 = two-cough response; Cr5 = five-cough response; CrTot = total number of coughs produced in response to 200 μ M capsaicin; H&Y = Hoehn and Yahr; P-A = penetration-aspiration scale; PD = Parkinson disease; UTC = urge to cough

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Aspiration pneumonia is a leading cause of death in people with idiopathic Parkinson disease (PD).¹⁻³ Although the pathogenesis of these infections is largely attributed to the presence of silent aspiration (aspiration without a reflex cough response), we know relatively little about reflex cough in PD. One important aspect of reflex cough is the urge to cough (UTC), a respiratory sensation that precedes the reflex cough. The UTC for induced reflex cough increases in a log-log linear fashion with increasing magnitude of a cough (tussigenic) stimulus.⁴⁻⁷ People with a history of aspiration pneumonia have comparable reflex cough thresholds to age-matched control subjects but demonstrate a blunted UTC at subthreshold levels of a tussigenic stimulus.⁸

Materials and Methods

This prospective study included 20 participants with mild to moderate PD. Participants were recruited from the University of Florida Center for Movement Disorders and Neurorestoration by consecutive referral to speech-language pathology over a 3-month period. Fellowship-trained movement disorders neurologists diagnosed PD using UK brain bank criteria.¹⁴ This study received ethical approval by the University of Florida Institutional Review Board (188-2012). All participants provided written informed consent prior to the initiation of any study procedures. They were tested within the window of optimized medication function (ie, 1 h after taking anti-PD medications). Inclusion criteria were (1) diagnosis of idiopathic PD, (2) Hoehn and Yahr (H&Y) stages II to IV, and (3) age 45 to 85 years. Exclusion criteria were (1) history of other neurologic disorders; (2) history of head, neck, or lung cancer; (3) history of chronic respiratory disorders/diseases; (4) smoking in the past 5 years; (5) uncontrolled hypertension; (6) minimal status examination score of at least 24; and (7) failed pulmonary function screening test (ie, FEV₁/FVC < 75%).

Cough Testing

Participants were outfitted with a face mask covering the nose and mouth. The face mask was coupled to a pneumotachograph and differential pressure transducer and had a side port with a one-way inspiratory valve for nebulizer connection. The nebulizer was a DeVilbiss T-piece (DeVilbiss Healthcare LLC) connected to a dosimeter that delivered an aerosolized solution during inspiration (delivery duration, 2 s). Participants completed a capsaicin challenge with three randomized blocks of 0, 50, 100, and 200 μ M capsaicin. The capsaicin was dissolved in a vehicle solution of 80% physiologic saline and 20% ethanol. The maximum concentration of 200 μ M has been identified as a suprathreshold concentration for eliciting the reflex cough in healthy participants.¹⁵⁻¹⁷ The cough airflow signal was recorded by a laptop computer through the PowerLab data acquisition system (ADInstruments Pty Ltd).

Participants were seated comfortably for an initial 30 s of quiet breathing to acclimate to the face mask. They were given the instruction, "Cough if you need to," prior to capsaicin delivery. The solution was automatically administered upon detection of an inspired breath, with a minimum of 1 min between each presentation of capsaicin during which time participants were provided water.

Although the literature suggests that both dysphagia and dystussia coexist in PD,^{9,10} few studies have tested reflex cough in PD,¹¹⁻¹³ and no studies have examined the relationship of reflex cough responses to swallowing ability. Leow and colleagues¹³ observed that the cough sensory threshold was not different for people with PD vs age-matched control subjects; however, Fontana et al¹¹ found slightly higher thresholds for people with PD. Neither of these studies included a metric for UTC or account for the influence of swallowing function on reflex cough outcomes. The goal of the present study was to test reflex cough thresholds and UTC ratings in participants with PD with and without dysphagia. We hypothesized that worsening dysphagia severity would result in significantly higher cough thresholds and reduced UTC ratings.

Swallow Testing

Swallowing was assessed by a certified speech-language pathologist. Participants were positioned in the lateral viewing plane while sitting in a chair and self-administered a 3-oz thin-liquid challenge bolus of barium sulfate contrast solution. Images were acquired with a Siemens radiographic/fluoroscopic unit (Siemens Corporation) and recorded at 30 frames/s. The selected swallowing outcome measure was quantified with the penetration-aspiration scale (P-A),¹⁸ a valid and ordinal eight-point assessment.

Outcome Measures

Cough Threshold: Total number of coughs produced in response to 200 μ M capsaicin (CrTot) was counted from the first cough epoch (defined as an initial cough and the subsequent cough reaccelerations following one inspiration) with each presentation of capsaicin. These measures were made from the recorded cough airflow signals. The concentration of capsaicin that elicited the reliable two-cough response (Cr2) was recorded and identified as the cough threshold. A reliable Cr2 was defined as at least two coughs produced within 30 s following presentation of the stimulus in two of three trials of that concentration.

Urge to Cough: Following each capsaicin trial, participants rated their UTC on a modified Borg rating scale of 0 to 10, where 0 was no UTC and 10 was maximal UTC. The median UTC ratings were plotted against capsaicin concentration on a log-log scale, and a linear regression line was used to fit the data. The slope of the line was used as a measure of UTC sensitivity to capsaicin and was compared in participants with and without (P-A score $\leq$ 2) dysphagia.

Statistical Analysis

Descriptive statistics were used to summarize the data. Spearman ρ correlations and regression analyses were used to assess the influence of PD severity (H&Y score), age, sex, disease duration, and dysphagia severity (P-A score) on UTC and CrTot. Sex, H&Y score, disease duration, and age were entered into the first step of the stepwise hierarchical regression model, with UTC or CrTot as the dependent variables. P-A score was entered in the second step to assess its contribution to the dependent variables above and beyond other person- and PD-specific factors. Differences in age and disease severity between participants with and without dysphagia were compared by Mann-Whitney *U* tests. The significance criterion was set at $P < .05$.

Results

Twenty participants (14 men), aged 49 to 81 years (average, 68 years) completed this study. Disease severity spanned from H&Y stage II to IV with Unified Parkinson’s Disease Rating Scale on medication scores between 9 and 48 (average, 24.4). Disease severity was not significantly associated with swallowing dysfunction (P-A score) ($r_s = 0.091$, $P = .704$). None of the participants had a history of aspiration pneumonia. Demographic information is included in Table 1.

Cough Threshold

All participants without dysphagia had a reliable Cr2 to 200 μ M capsaicin compared with only 50% of participants with dysphagia. Therefore, true cough thresholds could not be established for all participants. Regression analysis revealed that one factor, P-A score ($\beta = -1.359$, $P = .031$), explained 23.3% of the variance in CrTot [$R^2 = 0.233$, $F(1,18) = 5.459$, $P = .031$]. More specifically, as the P-A score (dysphagia severity) increased, CrTot decreased.

Urge to Cough

Regression analysis revealed that one factor, P-A score ($\beta = -0.593$, $P = .017$), explained 27.6% of the variance

in UTC [$R^2 = 0.276$, $F(1,18) = 6.857$, $P = .017$]. More specifically, as the P-A score (dysphagia severity) increased, UTC at 200 μ M capsaicin decreased.

The slope of the log-log linear line of best fit was 0.37 for the dysphagic group and 0.64 for the nondysphagic group (Fig 1). Five participants were scored as nondysphagic (P-A score ≤ 2), and 15 were scored as dysphagic. No significant differences in age ($P = .965$) or disease severity ($P = .603$) was found between groups. Participants without dysphagia had a median UTC of 5 at 200 μ M capsaicin compared with 2 in participants with dysphagia.

Discussion

Aspiration pneumonia is a leading cause of death in PD,¹⁻³ and although the pathogenesis of this infection is not completely understood, it is likely attributable to dysphagia and concomitant dystussia. Although our current clinical management focuses on rehabilitation of dysphagia with relative disregard for concomitant dystussia, our understanding of airway protection is evolving to include a continuum of behaviors serving to prevent (swallowing) and eject material from the airway (coughing). To our knowledge, the current study is the

TABLE 1] Demographic Information

Participant	Age, y	Sex	H&Y Score	Disease Duration, y	P-A Score	CrTot
1	68	Male	2	1	1	13
2	70	Male	2	2	1	11
3	71	Male	3	3	1	11
4	67	Female	2	11	2	16
5	69	Male	2.5	10	2	9
6	62	Male	2.5	13	3	3
7	49	Male	2	16	5	6
8	60	Female	4	9	5	14
9	60	Male	3	15	5	16
10	63	Male	2	5	5	0
11	65	Female	2.5	5	5	18
12	70	Female	2	18	5	3
13	70	Male	2	2	5	7
14	72	Male	2	8	5	0
15	73	Male	2	10	5	6
16	76	Male	2.5	14	5	8
17	77	Female	3	10	5	3
18	81	Female	2.5	2	5	4
19	66	Male	2	12	8	3
20	77	Male	3	11	8	0

CrTot = total number of coughs produced in response to 200 μ M capsaicin; H&Y = Hoehn and Yahr; P-A = penetration-aspiration scale.

Figure 1 – Median UTC ratings by capsaicin concentration in participants with and without dysphagia. The boxes indicate the first and third quartile of UTC scores, and the whiskers indicate the SE. Outliers are indicated by ● or ★. UTC = urge to cough.

first of reflex cough sensitivity and UTC in people with PD with and without known dysphagia. The results of this study support the hypothesis that both swallowing and cough function should be considered in the management of airway protection dysfunction in PD.

Dysphagia often is considered an inevitable consequence of PD. Dystussia has also been identified in PD,⁹⁻¹³ but has garnered less clinical research interest until recently. Pitts and colleagues^{9,10} found that voluntary cough expiratory airflow parameters are significantly decreased for people with PD that penetrated and/or aspirated. No studies have tested the relationship between reflex cough and swallowing function in PD. The behaviors of reflex cough and swallowing are similar in that they are both sensorimotor functions initiated by a specific oropharyngeal or laryngeal stimulus. In the case of swallowing, a specific bolus triggers the oropharyngeal swallow. In the case of reflex cough, the tussigenic stimulus, often aspirate material, induces the cough. Therefore, reflex cough (as opposed to voluntary cough) should better assist in elucidating the pathogenesis of aspiration pneumonia in PD given the high ecologic validity of the behavior.

Fontana et al¹¹ studied reflex cough in PD by using ultrasonically nebulized distilled water as the cough-inducing stimulus. They found a trend toward higher reflex cough thresholds in PD. Ebihara and colleagues¹² then studied reflex cough in female participants with early PD and advanced PD and age-matched control participants by using citric acid to induce cough. They

found that participants with advanced stage PD had higher cough thresholds than early stage PD and control participants. However, there was no significant difference in cough thresholds between early stage and control participants. Leow and colleagues¹³ studied reflex cough thresholds in participants with PD and healthy older adults and found no significant differences in cough thresholds across groups. Regression and correlation analyses from the current study revealed no relationship between disease severity and cough or swallowing outcomes, consistent with the results from the aforementioned studies. Interestingly, none of the studies of reflex cough in PD identified whether participants had dysphagia. It is possible that the presence of dysphagia may have better differentiated the groups, a hypothesis the current study findings support.

We found significant differences in the primary cough outcomes as a function of dysphagia severity. We chose 200 µM capsaicin as the highest concentration because it had been identified as a suprathreshold dose in previous studies.¹⁵⁻¹⁷ We were surprised to find that only 50% of the total sample had a reliable Cr2 to 200 µM capsaicin. Further inspection of the data revealed that all participants without dysphagia had a reliable Cr2, but only 33% of the participants with dysphagia had a reliable Cr2. In the future, 500 µM capsaicin will be included in our capsaicin cough challenge to more reliably establish a cough threshold for all participants.

In addition to absolute reflex cough thresholds, it is important to understand participants' perceived sensation to threshold and subthreshold cough stimuli. The UTC is a respiratory sensation that precedes the cough motor response.⁵⁻⁷ The urge, as the first component of the cognitive motivational system, brings the cough behavior to consciousness and, thus, allows for modulation of behavior.⁷ More specifically, the UTC requires discriminative and affective processing.^{4,19,20} Discriminative processing includes assessment of the characteristics of the cough stimulus, whereas the affective processing assigns emotional salience to the stimulus.^{4,19,20} In healthy control subjects, UTC is directly related to the intensity of the cough stimulus, resulting in a log-log linear relationship between capsaicin concentration and UTC.⁴⁻⁷

To our knowledge, this study is the first to examine UTC and the relationship among cough sensory threshold, UTC, and swallowing in a cohort of participants with PD. One study investigated the UTC and reflex cough thresholds elicited with citric acid in participants

with a history of aspiration pneumonia compared with age-matched control participants.⁸ Results revealed that Cr2 and the five-cough response (Cr5) were significantly higher for participants with a history of aspiration pneumonia. There was no significant difference in UTC ratings between groups at Cr2 or Cr5, but there were significant differences in UTCs between groups at one-half the Cr2 and Cr5 concentrations, demonstrating a blunting of UTC at subthreshold doses of citric acid for people with a history of aspiration pneumonia. We, therefore, hypothesized that the participants with dysphagia would have significantly reduced UTCs, specifically at subthreshold levels of capsaicin, which the results of this study support. In this case, participants with dysphagia showed a blunting of UTC at subthreshold stimuli compared with those without dysphagia. The slope of the log-log linear line of best fit was 0.37 for the dysphagic group and 0.64 for the nondysphagic group. In fact, both groups demonstrated a reduced UTC sensitivity compared with other healthy populations in which the UTC sensitivity (slope) has been closer to 2.¹⁶

The current study is not without limitations. Future studies should recruit larger numbers of participants to better assess other individual factors that might influence UTC and cough-related findings. Additionally, a tussigenic stimulus that is more similar to aspirate material and, therefore, more ecologically valid should be considered. Capsaicin was selected based on multiple studies having identified the stimulus as safe, reproducible, and measureable.²¹ In contrast to citric acid, capsaicin can be presented in succession with consistent, reliable results within one session and across sessions.²²

Fog, or nebulized distilled water, is another tussigenic agent that has been used in cough research, but no studies have investigated UTC in relation to fog.

Conclusions

The results of this study add to the body of literature, suggesting that various components of the cough behavior are impaired in people with PD, particularly in those with dysphagia. This study highlights the idea that the absent cough response in people with silent aspiration should not be considered as solely secondary to increased cough thresholds; it may also be due to a reduced UTC in response to a specific stimulus. Therefore, a reduced awareness of the presence of a tussigenic stimulus and a reduced response when the stimulus is perceived are possible. These factors likely combine to place patients at risk for uncompensated aspiration (silent aspiration), ultimately allowing the aspirated material to remain in the respiratory tract and serve as a focal point for infection.

Improvement in long-term airway protection in PD likely will require behavioral therapy targeting cough dysfunction. The UTC may be one of the most viable targets for cough rehabilitation given that the literature suggests that it can be behaviorally modulated.²³ To identify the best ways to upregulate the UTC, we must better understand the factors resulting in decreased UTC in PD. Therefore, future studies should focus on identifying the discriminative and affective components of UTC. Uncovering these issues could reveal specific therapeutic targets for the behavioral treatment of dysfunctional cough in PD.

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