Dysphagia (2012) 27:106–114
DOI 10.1007/s00455-011-9347-z

ORIGINAL ARTICLE

Changes in Chemosensitivity and Mechanosensitivity in Aging and Parkinson's Disease

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Received: 10 February 2010 / Accepted: 20 May 2011 / Published online: 1 July 2011

Abstract The risk of aspiration pneumonia in Parkinson's disease (PD) may be increased by sensory loss in the laryngopharynx and a reduced cough reflex. This study investigated changes in chemo- and mechanosensation with age and in PD and documented cough thresholds and cortical influences over cough. Single-breath citric acid inhalation cough challenge and flexible nasendoscopy were performed in 32 participants with idiopathic PD (mean age = 68.5 years, range = 45.8–82.5) and 16 healthy young adults (8 males, mean age = 25.1 years, range = 21.3–32.4), and 16 healthy elders (8 males, mean age = 72.8 years, range = 61.5–84.7) as controls. Individuals with PD had reduced sensation at the base of the tongue compared to age- and gender-matched counterparts ($p < 0.005$). All groups demonstrated lower natural cough thresholds than suppressed cough thresholds. No differences in natural cough thresholds were found across groups. Young adults demonstrated greater ability to suppress cough compared to healthy elders ($p = 0.021$). Tongue-base mechanosensory impairment in PD may account for vallecular residue and complaints of globus sensation. However, decreased cough response was not found to be a characteristic of PD. This study provided evidence for voluntary control of cough and the lack of decline of chemosensitivity with age or disease.

Keywords Cough reflex · Chemosensation · Mechanosensation · Citric acid · Aging · Parkinson's disease

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Parkinson disease (PD) is best-known as a disease affecting movement but sensory deficits are also frequent [1]. In PD, aspiration pneumonia is still the leading cause of mortality despite advances in the treatment of motor symptoms [2]. The lack of airway protection due to sensory deficits or diminished cough reflex has been postulated to be present in both PD and aging populations [3, 4]. Weakness of muscles involved in coughing has been demonstrated in PD [5, 6], and delayed recovery of the cough reflex has been postulated to increase morbidity and mortality in neurogenic disorders [7]. Less attention has been given to the contributions of sensory deficits in airway compromise during swallowing even though aspiration is considered to be important in the pathogenesis of aspiration pneumonia in older persons [4].

Biomechanical adduction of vocal folds in response to mechanical stimulation to the supraglottic mucosa is an important airway protection mechanism in preventing prandial aspiration [8]. Assessment of laryngopharyngeal mechanosensitivity poses difficulties as tactile stimulation

of the proximal pharyngeal area produces the gag reflex, which is uncomfortable for the patient and of little value in airway protection [9]. Two methods are currently used to assess distal laryngopharyngeal sensitivity. The first is fibre-optic endoscopic evaluation of swallowing with sensory testing (FEESST), utilizing a modified endoscope with an extra lumen or air pulse sleeve for the delivery of 2–10 mmHg of air to the aryepiglottic folds. The second method, fibre-optic endoscopic evaluation of swallowing (FEES), has been used since the 1980s and provides direct visualisation of the nasopharynx, oropharynx, larynx, and hypopharynx using a standard nasendoscope [10]. Mechanosensation may be assessed by lightly touching the pharyngeal walls, base of the tongue, or the epiglottis with the tip of the scope [11].

For both methods, observable patient reactions that suggest sensitivity include the laryngeal adductor response (LAR), eye blinking, tearing, throat clearing, swallowing, and coughing. Although FEESST has been invaluable in providing information regarding age and disease effects on laryngopharyngeal mechanosensation, the need for specialised equipment such as an air pulse generator makes the complete setup for FEESST expensive and less readily available. The second method of mechanosensitivity testing may be more practical in the clinical setting.

There has been no evaluation of standard FEES for comparing mechanosensitivity in age and disease. Previous research, including that which evaluated FEESST, has reported the loss of sensation in the pharynx and larynx after a neurological event such as stroke [12], but data on reduced laryngopharyngeal sensation in PD is lacking.

Closely related to vocal fold adduction as a means of airway protection is the ability to mount a reflexive cough in the event of aspiration. Although up to six different types of respiratory responses have been identified in humans when the tracheal mucosa is stimulated [13, 14], it is undisputed that of these, coughing may be the single most important defence mechanism for airway clearance. In elders, a decline in physical function due to sarcopenia—a reduction in muscle strength and power—is detrimental to the ability to generate maximal expiratory forces required during coughing [15]. Pitts et al. [6] demonstrated significant differences in various voluntary cough measures between PD patients who exhibited laryngeal penetration/aspiration compared to those with PD who did not, with better airway protection observed in those with more effective cough.

Chemosensory investigations are also limited. When the motor components of cough were compared to sensory aspects of cough using inhalation of citric acid, Ebihara et al. [3] found that in the early stages of PD, motor control was primarily impaired with preservation of chemosensation. In the later stages of the disease, however, both motor and sensory components of cough were affected. Citric acid cough thresholds in individuals with PD were significantly higher when compared to healthy controls, suggesting reduced sensation, especially in the later stages of PD.

Inhalation cough challenge is a means of evaluating laryngopharyngeal chemosensation [7] and has been used in the investigation of the cough reflex and antitussives for over 50 years [16]. Subsequent refinement of techniques has allowed the administration of inhaled irritants to be honed into a useful tool for assessing chemosensation and cough reflex [17]. Despite this progress, two concerns persist. First, the cough reflex can be consciously suppressed or modified depending on instructions given. It is debated whether the cough "reflex" is truly reflexive [18]. In studies that document only natural cough response, the sensitivity to tussigenic agents may vary widely because participants may suppress coughing without the investigator's knowledge. The second concern is the lack of a universal standard when conducting cough challenge testing. Normal values for a particular tussive agent have not been established, making comparisons between centres difficult [19]. Despite these hurdles, researchers are in general agreement that inhalation cough challenge may be a potentially useful tool in the clinical setting as chemosensitivity is imperative for the generation of a reflexive cough [19, 20].

The aim of the present study was threefold. First, we evaluated cortical influences over cough. Second, we investigated the effect of aging and PD on reflexive cough using the inhalation cough challenge. Third, we examined mechanosensory changes in aging and PD by identifying the laryngeal adductor response (LAR) using a qualitative method of sensory testing.

Materials and Methods

Participants

Following approval from the regional Health Ethics Committee, a total of 64 participants were recruited to the study. Participants with the diagnosis of idiopathic Parkinson's disease (mean age = 68.5 years, range = 45.8–82.5) were recruited by advertisement from a movement disorders clinic. The patient participants were staged using the Hoehn and Yahr (H-Y) scale [21], with 16 identified as having "earlier PD" (H-Y $\leq$ stage 2) and 16 identified as having "later PD" (H-Y stage $\geq$ 2.5). None had a history of other neurological or movement disorders (e.g., stroke, progressive supranuclear palsy, Huntington's disease). Patient medication regimen was stable, without changes in the month prior to participation in the study.

In addition to the PD participants, 16 healthy young adults (8 males, mean age = 25.1 years, range = 21.3–32.4) and 16 healthy elders (8 males, mean age = 72.8 years, range = 61.5–84.7) were recruited by advertisement. Exclusion criteria for all groups included the presence of significant central neurological disorders such as stroke, dementia, swallowing impairment (unrelated to PD), pulmonary disease (e.g., asthma, chronic obstructive pulmonary disease), and head and/or neck injury or surgery. Potential participants on antitussive medication for coughs, colds, and hay fever allergies were excluded, as were those with a current upper/lower respiratory tract infection. Participants with a history of smoking had ceased smoking at least 5 years prior to participating in this study.

Participants were invited to a swallowing research laboratory for a single-visit assessment session of airway protection mechanisms. As patient participants were assessed during the "On" phase of their medication, the studies were scheduled around the time of their best performance, generally within a half hour of their last dose of medication.

Mechanosensory Testing

Nasendoscopy was used to evaluate pharyngeal sensitivity [22]. A 3.5-mm Welch Allyn® RL-150™ nasendoscope was connected to the Digital Swallowing Workstation (DSW) (Model 7200, Kay Elemetrics Corp., Lincoln Park, NJ) which captured and stored entire evaluations for offline analyses. After lubricating the endoscope with K-Y Jelly®, the endoscope was inserted into the patient's nostril, with the choice of nostril at the discretion of the participant. As far as possible, the endoscope followed the inferior turbinate of the nasal cavity. Once the posterior pharyngeal wall was in view, with the scope still in the nasal cavity, participants were asked to phonate the syllables "duh-nuh" several times and to perform a saliva swallow to assess velar elevation. They were instructed to breathe through the nose whilst the endoscope was advanced into the hypopharynx. Most laryngeal structures were visible with the scope just above the epiglottis. Participants were instructed to perform a cough and a swallow and to vocalise /i:/ for 2–3 s as an assessment of voluntary vocal fold adduction. No participant had difficulty completing any preliminary task nor showed evidence of velar or vocal fold impairment. As such, analyses of these features are not included in this report.

Qualitative sensitivity testing of the pharynx was completed using a protocol described by Langmore and Aviv [11]. Using this method, the tip of the endoscope was used to provide light touch on the left and right sides of the base of the tongue, posterior pharyngeal wall, and aryepiglottic fold. This procedure allowed for evaluation of the presence or absence of the LAR, a brief, brainstem-mediated adduction of the vocal folds [8]. Other responses such as facial grimacing, participant feedback, cough, and/or swallow were also taken to be positive responses for pharyngeal sensitivity [11].

Chemosensory Testing

Inhalation cough challenge was completed using a method similar to that described by Morice et al. [19]. In that study, citric acid was diluted in 0.9% sodium chloride to obtain ½ log concentrations of citric acid ranging from 1 mM to 1 M. This translated into concentrations of 1, 3, 10, 30, 100, and 300 mM and 1 M. A small pilot study on six healthy participants prior to conducting this study showed that no participants coughed at 1 or 3 mM. In order to obtain concentrations that were more evenly spaced and that would eliminate floor or ceiling effects without unnecessarily extending the testing time, citric acid was diluted in 0.9% sodium chloride to obtain concentrations of 10, 30, 100 mM (½ log), 177.83, 316.23, 562.34 mM (¼ log), 1, 1.2, 1.4, 1.6, 1.8 and 2 M (linear).

The PulmoMate Compressor/Nebuliser by deVilbiss (model 4650I) with a predetermined flow output of 8 L/min was used to deliver different concentrations of citric acid in the inhalation cough challenge. Micro Mist Disposable Nebulizer pots (Medical code A7003) with 7 ft of tubing were used to deliver the citric acid.

Participants were told that they were participating in a cough challenge and that the vials contained different concentrations of citric acid. Some of the inhalations may make them cough and some would not. They were initially told to "cough when you feel the need to cough; do not cough if you do not feel the need to cough." This was to identify the natural cough threshold. The natural cough threshold was identified when participants coughed at least twice within the first 10 s in at least two of the four inhalations (50%) of that dose. When the natural cough threshold was identified, participants were then told that the test would continue with new instructions. From that time forth, they were instructed to "try to suppress the cough as best you can." The suppressed cough threshold was reached when participants coughed at least twice in at least two of four inhalations (50%) of that dose. Two concentrations of citric acid were recorded for analysis: the level at which the participants spontaneously coughed (natural cough) and the level at which participants could no longer inhibit a cough (suppressed cough).

Delivery of citric acid employed the full exhalation–full inhalation method [23]. With a nose clip in place, participants were instructed to place the mouthpiece of the nebuliser kit into their mouths to form a good seal. When the nebuliser was turned on, they were asked to fully exhale to

residual volume and then fully inhale to total lung capacity. The DeVilbiss nebuliser had a constant flow rate of 8 L/min. Participants were coached on a placebo (0.9% NaCl) dose until proper technique was obtained. Citric acid was administered in incremental concentrations, with three placebo vials randomly interspersed to increase challenge blindness. Each dose was administered four times, with a 30-s interval between each inhalation to prevent tachyphylaxis. The number of coughs in the first 10 s after each inhalation was recorded manually. The entire cough challenge study was recorded on an audio-visual system for offline analysis.

Statistical Procedure

Mechanosensation

Binary "yes" or "no" choices were entered as positive response or negative response to tactile stimulation using the tip of the endoscope. Bilateral base of tongue (BOT), posterior pharyngeal wall (PPW), and aryepiglottic folds (AEF) were assessed by the primary author and responses were coded using the agreed consensus of two speech-language pathologists familiar with endoscopy. The χ^2 test for independence was used to analyse observed and expected counts for the presence or absence of sensation. Group (young adults, elders, and PD) and sensitivity (yes or no) were used as the categorical variables. Due to the small sample size, p values from Fisher's exact test [24] were used to determine significance.

Chemosensation

The inhalation cough challenge sessions were video-recorded and the numbers of natural and suppressed coughs were determined by manually counting the number of coughs generated. A random 25% of the entire data set was reanalysed by the primary rater (LP) and two independent raters in order to determine the intraclass correlation coefficients for intra- and interrater reliability. Mann–Whitney U-tests were conducted to compare concentrations at which natural and suppressed coughs occurred between healthy young adults and elders. Wilcoxon signed-rank tests were conducted to compare concentrations at which natural and suppressed coughs occurred between elders and those with PD. Group (young, elders, and PD) was entered as the independent variable and citric acid concentration (where 1 = 10 mM, 2 = 30 mM, 3 = 100 mM, 4 = 178 mM, 5 = 316 mM, 6 = 562 mM, 7= 1 M, 8 = 1.2 M, 9 = 1.4 M, 10 = 1.6 M, 11 = 1.8 M, 12 = 2 M) for natural and suppressed coughs was entered as the dependent variable.

Results

A total of 32 participants with the diagnosis of idiopathic Parkinson's disease (mean age = 68.5 years, range = 45.8–82.5) were recruited, with 16 being "earlier PD" (H-Y $\leq$ stage 2) and 16 "later PD" (H-Y stage $\geq$ 2.5). In addition, 16 healthy young adults (8 males, mean age = 25.1 years, range = 21.3–32.4) and 16 healthy elders (8 males, mean age = 72.8 years, range = 61.5–84.7) were recruited.

Mechanosensation

The χ^2 analysis results are presented in Table 1. No significant difference in laryngopharyngeal mechanosensitivity was identified between healthy young adults and healthy elders at all six test sites. Participants with PD demonstrated a significantly reduced sensation to mechanosensation at bilateral base of tongue compared to healthy elders. No significant differences were found between those with earlier PD and those with later PD. A nonsignificant trend toward decreased sensation for all other test sites in PD compared to healthy elders was noted. Specifically, a further decrease of sensation ranging from 10% at the left aryepiglottic fold to 34% at the right posterior pharyngeal wall was seen in individuals with PD.

Chemosensation

Intraclass correlation coefficient revealed high reliability, with $r = 0.997$ for both intra- and interrater reliability. For both healthy young adults and elders, natural cough threshold (M = 4.9, SD = 2.7) was always significantly lower than the suppressed cough threshold [(M = 8.2, SD = 3.5), $Z = -4.7$, $p = 0.001$]. Detailed analysis using the Mann–Whitney test showed no difference between healthy young adults and elders for natural cough thresholds ($Z = -1.7$, $p = 0.102$) but showed a significant difference in suppressed cough thresholds ($Z = -2.4$, $p = 0.021$), with young adults demonstrating greater ability to inhibit cough (Fig. 1). The Wilcoxon signed-ranks test showed no difference for natural cough thresholds between healthy elders (M = 4.06, SD = 1.88) and those with PD [(M = 4.81, SD = 2.51), $Z = -1.03$, $p = 0.306$]. There was also no difference for suppressed cough thresholds between healthy elders and those with PD ($Z = -0.475$, $p = 0.635$).

For patients in the earlier and later stages of PD, natural cough threshold (M = 4.69, SD = 2.25) was significantly lower than the suppressed cough threshold [(M = 5.97, SD = 2.51), $Z = -3.87$, $p = 0.001$]. In addition, the Mann–Whitney test showed no difference between those with earlier PD (M = 4, SD = 1.2) and those with later

Table 1 Percentage positive and negative responses for mechanosensitivity

	Fisher's exact	Site of test	Group	Positive response (%)	Negative response (%)
Healthy, young adults and healthy elders	0.484	Right BOT	Young	87.5	12.5
			Elders	100	0
	1	Left BOT	Young	93.8	6.3
			Elders	100	0
	1	Right PPW	Young	93.8	6.3
			Elders	87.5	12.5
	0.333	Left PPW	Young	93.8	6.3
			Elders	75	25
	0.484	Right AEF	Young	100	0
			Elders	87.5	12.5
	1	Left AEF	Young	100	0
			Elders	93.8	6.3
Age- and gender-matched elders and PD[a]	0.004*	Right BOT	Elders	100	0
			PD	53.8	46.2
	0.004*	Left BOT	Elders	100	0
			PD	53.8	46.2
	0.092	Right PPW	Elders	87.5	12.5
			PD	53.8	46.2
	0.270	Left PPW	Elders	75	25
			PD	53.8	46.2
	0.624	Right AEF	Elders	87.5	12.5
			PD	75	25
	0.560	Left AEF	Elders	93.8	6.3
			PD	83.3	16.7
Earlier PD and later PD[b]	0.707	Right BOT	Earlier	62.5	37.5
			Later	50	50
	1	Left BOT	Earlier	50	50
			Later	50	50
	0.459	Right PPW	Earlier	50	50
			Later	66.7	33.3
	0.705	Left PPW	Earlier	56.3	43.8
			Later	66.7	33.3
	0.092	Right AEF	Earlier	87.5	21.5
			Later	53.8	46.2
	0.632	Left AEF	Earlier	87.5	12.5
			Later	76.9	23.1

BOT base of tongue, *PPW* posterior pharyngeal wall, *AEF* aryepiglottic fold

* Significant at $p \leq 0.05$, determined by McNemar χ^2 test

[a] Elders age- and gender-matched to PD across severity levels

[b] Earlier PD = Hoehn-Yahr $\leq$ stage 2; later PD = Hoehn-Yahr $\geq$ stage 2.5

PD ($M = 5.4$, $SD = 2.8$) for natural cough thresholds ($Z = -1.427$, $p = 0.171$ and suppressed cough thresholds ($Z = -1.071$, $p = 0.305$) (Table 2).

When the Wilcoxon signed-ranks test was conducted to investigate the differences in citric acid concentration used between natural and suppressed coughs, results did show a significant difference in concentration between cough thresholds (natural and suppressed) for elders and those with PD. Specifically, there was a greater difference in concentration between natural and suppressed coughs for elders ($M = 2.44$, $SD = 1.79$) compared to those with PD [($M = 1.19$, $SD = 1.22$), $Z = -1.97$, $p = 0.049$], suggesting greater ability for healthy elders to suppress cough. Mann–Whitney U showed no statistical difference between cough thresholds for young adults and elders ($Z = -1.66$, $p = 0.098$) or for cough thresholds in patients with earlier PD and later PD ($Z = -1.13$, $p = 0.259$).

Discussion

This research provides new information regarding airway protection mechanisms in PD. We demonstrated a degree of voluntary control of cough in all patients with PD, elder

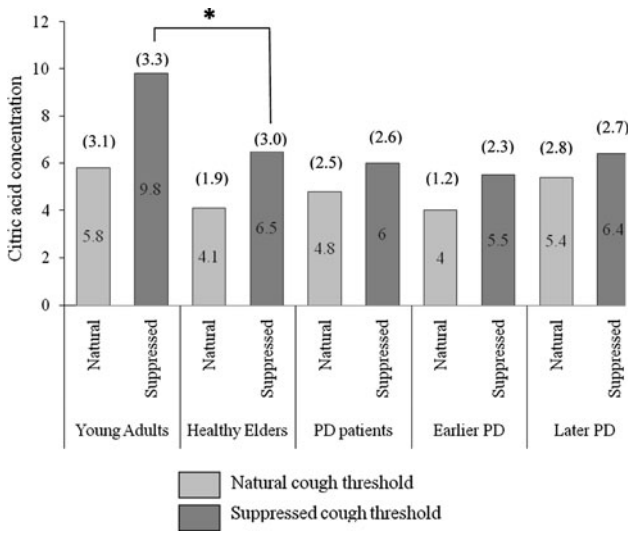

Fig. 1 Means and standard deviations for natural and suppressed cough across groups. 1 = 10 mM, 2 = 30 mM, 3 = 100 mM, 4 = 178 mM, 5 = 316 mM, 6 = 562 mM, 7 = 1 M, 8 = 1.2 M, 9 = 1.4 M, 10 = 1.6 M, 11 = 1.8 M, 12 = 2 M. *Significant difference ($p = 0.021$) determined by Mann–Whitney test

controls, and young controls. We provided some evidence that nasendoscopy with qualitative mechanosensory testing was sensitive enough to detect differences between healthy adults and those with PD. Finally, our data also suggest that mechanosensation but not chemosensation is impaired in PD, a disease associated primarily with motor deficits and where sensory loss is often overlooked.

The first aim of the study was to demonstrate the voluntary control of cough. We demonstrated a degree of voluntary control of cough in all patients with PD and all controls. For all participants regardless of age, disease and disease severity, suppressed cough response was significantly higher than natural cough response, lending strong support for the voluntary control of cough described by Hutchings et al. [25]. The ability to voluntarily control coughing has several important clinical implications. Very importantly, it allows clinicians to reinforce to patients that while coughing can be suppressed at will, it can also be more efficient given the right training. Using expiratory muscle strength training (EMST), several research groups have found improvements in cough efficacy in PD with direct improvements in the ability to protect the airway after EMST [6, 26]. This training translated into an improvement in penetration–aspiration scale scores [27], reflecting better airway protection.

We also examined mechanosensory changes in aging and PD by identifying the LAR using a qualitative method of sensory testing. Using this method, we proved that nasendoscopy with qualitative mechanosensory testing was sensitive enough to detect differences between healthy adults and those with PD. Mechanosensory loss was significant at BOT of those with PD, which may account for the common finding of vallecular residue [28]. In addition to the novel method of testing laryngopharyngeal chemosensation, this is the first study to use qualitative sensory testing as described by Langmore and Aviv [11] for the assessment of laryngopharyngeal mechanosensation. Key findings from this analysis would support the conclusion that sensation remains intact as long as there is no evidence of neurological disease, as is the case with healthy participants in this study. Individuals with PD, however, demonstrate sensory loss at the base of tongue compared to their healthy counterparts.

The third aim of the study was to investigate the effect of aging and PD on reflexive cough using the inhalation cough challenge. This study revealed that young adults demonstrated significantly higher suppressed cough threshold than healthy elders. Although we hypothesised that patients who were in the later stages of PD may have decreased cough sensitivity due to disease progression, results of the present study did not support this hypothesis. Even individuals with PD with more severe symptoms, and hence implicit aspiration risk, have similar natural cough responses compared to those with less severe symptoms. When instructed to suppress cough, elders demonstrated significantly lower suppressed cough threshold compared to young adults. Those with PD are less able to suppress cough compared to their age- and gender-matched counterparts based on the significantly smaller distance between natural and suppressed coughs. It is plausible that the need

Table 2 Means and standard deviations for natural and suppressed cough threshold concentrations for each group

	Young adults		Healthy elders[a]		PD patients[a]		Early PD[b]		Late PD[c]	
Groups	M	SD	M	SD	M	SD	M	SD	M	SD
Natural cough threshold	5.8	3.1	4.1	1.9	4.8	2.5	4	1.2	5.4	2.8
Suppressed cough threshold	9.8	3.3	6.5	3	6	2.6	5.5	2.3	6.4	2.7

M mean, *SD* standard deviation

[a] Elders age- and gender matched to PD across severity levels

[b] Earlier PD = Hoehn-Yahr ≤ stage 2

[c] Later PD = Hoehn-Yahr ≥ stage 2.5

for airway protection is more important than the call to stifle coughing. This hypothesis, in addition to the finding that elders demonstrate a trend toward heightened natural cough sensitivity, may suggest increased airway protection with age and disease.

Our study demonstrated that a differentiation between healthy adults and those with PD was still possible using qualitative sensory testing, supporting other findings using FEESST in neurological disorders. It is acknowledged that there is no way to quantify sensory loss with the method used in this study. However, similar criticism may be applied to FEESST. As the highest limit of deliverable pressure is 10 mmHg, there is also no quantification of severe sensory loss above 10 mmHg. In a different study, Phua et al. [29] demonstrated that those with cough and reflux disease have impaired laryngopharyngeal mechanosensitivity and many patients did not respond to air pulse stimulation even at the highest pressure (10 mmHg), illustrating that quantification of sensory loss beyond 10 mmHg is not possible.

There are several limitations identified in this study. It may be argued that sensory testing with FEES alone in the absence of a means to quantify sensation or sensory loss is not a valid test of sensation. It is acknowledged that FEES with qualitative sensory testing may not be sensitive enough to detect small sensory changes. Nevertheless, it may be useful to detect larger or gross sensory loss. Even though mechanodesensitisation may be expected and has been documented with age using FEESST [30], it is of note that the difference between the youngest group (age 20–40 years) and the oldest group ($\geq$61 years) was less than 1 mmHg. There were no attempts to correlate age-accompanied sensory changes to swallowing processes in Aviv's study [30], making it difficult to establish if sensory loss of less than 1 mmHg between young adults and elders also translated to airway protection compromise.

The clinical importance of assessing reduced laryngopharyngeal sensation is heightened by the suggestion that sensory loss may be associated with an increased risk of aspiration pneumonia. Thus, one might predict that patients with reduced sensation would often be silent aspirators. However, Aviv et al. [31] reported that 9 of 10 patients who aspirated on VFS had bilateral laryngopharyngeal sensory deficits but only 1 of these 9 patients demonstrated silent aspiration. From this observation Langmore [32] highlighted that this discrepancy is because silent aspiration implies subglottic insensitivity (recurrent laryngeal nerve), whereas FEESST assesses the integrity of the supraglottic region innervated by the SLN. Perhaps this is why a direct comparison between mechanosensation and silent aspiration has yielded poor correlations. Although supraglottic sensation may not directly relate to risk of prandial airway compromise and silent aspiration, decreased sensitivity in the laryngopharynx may still impact airway protection indirectly. Patients with postswallow residue may not be able to respond to pharyngeal residue, thereby risking postswallow aspiration.

As FEESST relies on the observation of a motor response such as vocal fold adduction as an indication of laryngopharyngeal sensory integrity, it cannot fully elucidate whether the abnormality lies in the sensory limb or the motor response. Several factors have been carefully controlled in this study to allow for good hypotheses that help to tease out the underlying pathophysiology. While an assessment of mechanosensitivity using the LAR does rely on a motor response, the LAR is thought to be a brainstem-driven response, one that does not require a conscious activation of the motor cortex and thought to be impervious to cortical influences. In addition to the LAR, we looked for other signs of sensation such as verbal feedback from the participant, tearing, or grimacing. We then hypothesised that if the LAR is absent but the patient acknowledges the sensation in other ways such as tearing and/or facial grimacing, it would signal loss of motor responses in the presence of preserved sensation. The absence of LAR *plus* the absence of all other symptoms would signal total sensory loss.

The inhalation cough challenge was, in the present study, carried out using the full exhalation followed by full inhalation method [23]. Identical instructions were given to all participants, but in the absence of a dosimeter, neither inhalation rate nor dose was tightly controlled. Results of the present study are interpreted in light of this limitation. As the rate of inhalation has been known to affect the deposition of the tussigenic agent with lowered cough thresholds at a slower inhalation rate, it would be important for future studies to use a dosimeter to control the rate and dose of tussigenic agents [33].

The absence of a significant difference in chemosensation in PD may be due to the dichotomous grouping of the patients into "earlier PD" (H-Y $\leq$ stage 2) and "later PD" (H-Y stage $\geq$ 2.5). When there is no substantial difference in H-Y stages, any differences in patients' performance may have been too small to be reflected in the assessment conducted. As some deterioration in function may not be seen until H-Y stage 5 [3], cross-sectional comparisons between patients in early (H-Y stage 1), middle (H-Y stage 3) and late (H-Y stage 5) stages would be recommended for future studies.

Only one study has reported a significant difference in early- and late-stage individuals [3], but that study was methodologically different from this study in three ways. First, early-stage patients in Ebihara et al.'s study consisted of patients in H-Y stages 2 and 3, while patients allocated to the late-stage group were in H-Y stage 4. Our study dichotomised severity level by categorising H-Y stage $\leq$2

as early stage and those in H-Y stage $\geq$2.5 as late stage. Nonsignificant trends between those in the earlier and later stages in our study may be accounted for by the inclusion in the later group stage 3 patients who may not be as insensate as those in stage 4. Second, Ebihara et al. [3] used a fixed-time inhalation challenge of 1 min per citric acid concentration. The present study followed the published protocol by Morice [34], using the single-inhalation dose-response method. Finally, only females were assessed in the Ebihara et al. study, whereas the present study included male participants. This study included 65% males and 35% females, comparable to literature that report 61 and 39% males and females with PD [35].

In conclusion, this study was the first to assess both chemo- and mechanosensation with respect to age and PD, a disease associated with motor deficits where sensory loss is often overlooked. There continues to be evidence for voluntary control of cough. Results of this study suggest that PD differentially affects chemosensory and mechanosensory pathways, with mechanosensation affected before chemosensation. This study was also the first to document that nasendoscopy with qualitative mechanosensory testing was sensitive enough to detect differences between healthy adults and those with PD, which has implications for the perception of residue. There is a need for future studies to correlate the use of qualitative sensory testing to FEESST in order to achieve a more objective measurement of sensation. In addition, future studies would need to correlate chemo- and mechanosensation to swallowing function to establish and quantify how much these contribute to overall airway protection.

Acknowledgments The authors thank Associate Professor Chris Frampton from the Christchurch Consultancy Group for his advice on statistical analyses.

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