Movement Disorders
CLINICAL PRACTICE
RESEARCH ARTICLE

Lung Function Testing *On* and *Off* Dopaminergic Medication in Parkinson's Disease Patients With and Without Dysphagia

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Abstract: **Background:** Swallowing function in individuals with Parkinson's disease (PD) can be negatively affected by dopaminergic medication with associated inhibition of brainstem reflexes. Three different "swallowing-safety" profiles of PD patients were previously observed, classified according to swallowing safety *on* and *off* levodopa.
Methods: Here, we investigated the effects of L-dopa on pulmonary function tests (PFTs) on 26 individuals with PD from the three different swallowing-safety profiles. PFTs results were compared to predicted values and direct comparisons between the groups with or without dysphagia were performed with nonparametric statistical tests (i.e., Kruskal–Wallis).
Results: A short (12-hour) withdrawal from L-dopa did not result in any significant changes in PFTs, and no differences on PFTs results were observed between the different dysphagic groups the *on* and *off* L-dopa state. No correlation was observed between the PFTs results with swallowing safety profiles of PD patients.
Conclusions: Although deglutition seems to be at least partially affected by dopaminergic repletion, dopaminergic mechanisms do not seem to be responsible for PD patients' performance in PFTs.

Parkinson's disease (PD) is the most common neurodegenerative disorder after Alzheimer's disease and its prevalence increases with age.[1] Even in early years after PD diagnosis, swallowing impairments and respiratory difficulties can be observed with objective assessments.

A meta-analysis on the prevalence of dysphagia reported that although subjective (self-reported) dysphagia occurred in 1 of 3 PD patients, objectively measured dysphagia was much higher with a rate of 4 of 5.[2] The symptoms of dysphagia can be present during the oral and/or pharyngeal phases of swallowing. Correlations between dysphagia and PD severity were found by some,[3–5] whereas others using different definition for dysphagia did not find a clear association.[6,7]

Similarly, pulmonary dysfunction has been associated with increased morbidity and mortality[8] and can be detected in the early stages of PD,[9] whereas serious complications occur later in the disease course. Importantly, aspiration pneumonia is one of the most common causes of death in PD.[10]

These altered pulmonary mechanics, along with the lack of coordination between respiratory and swallowing mechanisms, are proposed to significantly increase the risk of laryngeal penetration and aspiration.[11] From a mechanistic perspective, there is an association between respiration and swallowing. In the brainstem area, the motor neurons forming the swallowing and respiration central pattern generators are thought to reside in close proximity.[12–14] Therefore, not only is there the notion for similar neuronal pathways for the sensorimotor control, but also there are shared physiological structures in the oropharynx for respiration and swallowing. Moreover, swallowing also causes a resetting of the respiratory rhythm demonstrating a modification of respiratory cycling by swallowing.[15]

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However, controversy exists over the effects of dopamine replacement with levodopa on dysphagia, with some cases reporting no effect[16] and others an adverse effect.[7,17,18] Similarly, the effect of L-dopa on pulmonary dysfunction is controversial with a meta-analysis reporting improvement in forced vital capacity (FVC) and peak expiratory flow (PEF), but not in forced expiratory volume in 1 second (FEV1).[19]

The aim of this study was to investigate whether there are differences in pulmonary function tests (PFTs) between dysphagic and nondysphagic PD patients during both *on* and *off* dopaminergic medication states.

Patients and Methods

Twenty-six subjects (17 male, mean age: 65 ± 9 (±standard error of the mean), mean time on L-dopa 5 ± 1 years), with clinically confirmed PD diagnosis according to the UK Parkinson's Disease Society Brain Bank[20] and H & Y[21] scores of II to IV while *on* medication, were recruited from movement disorder clinics at Salford Royal NHS Foundation Trust after provision of their written informed consent. The data in this article were generated during the study published by Michou et al.[18] The study was approved by the Greater Manchester South Research Ethics Committee.

The individuals were asked to withhold from L-dopa for at least 12 hours before the assessments in the morning (*off* state). The pulmonary function trials were conducted using closed-loop spirometry (MicroDL; CareFusion Ltd, Basingstoke, UK) and a respiratory pressure meter (Micro RPM; CareFusion), according to the guidelines.[22] Before initiating the procedure, all subjects were instructed by an experienced and blinded clinical researcher (M.L.H.). This included a practical demonstration and a trial run. Patients were seated in a comfortable position and appropriately rested between tests, according to recommended guidelines.[22] For the respiratory muscle strength, the following were tested and were presented in units of cmH_2O gauge pressure: maximal sniff nasal inspiratory pressure (SNIP); maximal inspiratory pressure (MIP); and maximal expiratory pressure (MEP). The additional PFTs included: FEV1 and FEV1 (%); FVC PEF and PEF (%); and forced expiratory ratio (FEV1/FVC).

The initial spirometry tests were followed by videofluoroscopy (VFS; lateral view). Subjects were asked to perform 6 (5-mL) swallows of each of thin-like liquids and pudding-thick liquid (puree). All boluses (barium sulphate; EZ-HD, E-Z-EM, London, UK) were presented to the patients randomly to control for fatigue and bolus presentations. For all participants, the assessment sessions started at the same time of the day to control for circadian changes. The above PFTs and respiratory muscle strength assessments were then repeated 1 hour post-L-dopa administration.

Statistical Analysis

First, we compared the PFTs to predicted and normative values. We calculated the predicted values on an individual basis, based on equations available and standardized elsewhere.[23–26] Subsequently, we compared the predicted to the acquired values from this study using intraclass correlations for absolute agreement, thus introducing case-by-case analysis while minimizing the effect of parameters such as age and sex.

Swallowing safety was evaluated using the penetration aspiration (PA) scale[27] describing airway compromise for each swallow. Moreover, the residue in valleculae and pyriform sinuses, as well as the repeated "clearing" swallows were also recorded. Based on previous multiple regression analysis,[18] the cut-off point for an individual to present dysphagia was the presence of at least one incidence of laryngeal penetration (PA score of 3) in a single swallow and one swallow with a residue of more than 50% of the bolus in pyriform sinuses. Three groups were identified based on the different swallowing behavioral effects of L-dopa on VFS: patients with swallowing impairments both *on* and *off* medication (SI); patients with impairments only *on* medication (SIon); and patients with no swallowing impairments (NSI).[18] The L-dopa equivalent dose (LED) was calculated for each participant.[28] Data are expressed as mean ± standard deviation (SD). We also examined the relationship between PFTs and PA scores with Spearman's Rho correlation analysis. For this reason, we combined the groups of SIon and SI into one: "dysphagic" group.

Between groups, comparisons of parameters, such as age, PD duration, and LED, as well as PFT results, were performed with the use of nonparametric tests. In particular, we used Kruskal–Wallis to detect significant differences between the variances of the groups and Mann-Whitney nonparametric tests to compare between pairs of groups (NSI vs. SI, SI vs. SIon, and SIon vs. NSI). Within each group (NSI, SIon, and SI), we compared their responses *on* versus *off* with Wilcoxon's signed-rank test.

Multiple comparisons corrections were performed with the step-down Homs-Sidak technique (StataIC version 12; StataCrop LP, College Station, TX) on the results acquired. Significance was set at $P < 0.05$.

Results

All participants completed all trials with no adverse events. From the comparison of the acquired PFTs to calculated predicted values, we observed that our group of PD participants showed low agreement in only the three following parameters: MEP, MIP, and SNIP (Table S1).

Following the grouping of patients based on their swallowing safety and efficacy, we compared the mean age, duration of PD, and LED across the three groups (Kruskal–Wallis nonparametric test). Mean age and PD duration did not differ among groups (Table 1). However, LED was significantly higher for the SIon and SI groups compared to the NSI group (SIon vs. NSI: $P = 0.011$, $U = 7$; SI vs. NSI: $P = 0.043$, $U = 23.5$, Mann–Whitney test; Table 1). In order to check whether there is an association between the swallowing performance and lung function testing, we grouped together the SIon and SI groups and we correlated the groups' PA scores to lung function tests. However, there was no significant correlation between any of the parameters and PA scores.

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TABLE 1 Pulmonary function tests and respiratory pressures of individuals with PD within the three groups, classified according to swallowing *on* and *off* L-dopa

Groups Mean ± SD		NSI	SIon	SI	Statistical Significance (*P* values)
Age, years		64 ± 3	62 ± 3	68 ± 6	ns
Sex, male		5/10	5/6	7/10	
PD duration, years		4.8 ± 0.7	7.2 ± 1.4	8.5 ± 1.8	ns
H & Y score		2.1 ± 0.1	2.5 ± 0.1	2.4 ± 0.2	ns
LED		688 ± 239	1,130 ± 405	958 ± 312	$P = 0.027$, $\chi^2 = 7.2$
SNIP	*off*	61.7 ± 49.1	84.2 ± 34.2	47.5 ± 35.2	ns
	on	58.2 ± 50.9	73.7 ± 39.9	55.6 ± 37.2	ns
MIP	*off*	68.5 ± 31.1	88.2 ± 47.9	52.8 ± 35.7	ns
	on	69.4 ± 26.6	90.2 ± 60.2	41.8 ± 42.6	$P = 0.013$, $\chi^2 = 8.6$ (corrected: $P = 0.195$)
MEP	*off*	86.6 ± 29.3	103.2 ± 66.0	61.6 ± 27.8	ns
	on	81.1 ± 29.3	117.5 ± 46.4	64.3 ± 23.2	ns
FEV1	*off*	2.4 ± 0.85	3.2 ± 0.5	2.1 ± 0.6	$P = 0.029$, $\chi^2 = 7$ (corrected: $P = 0.435$)
	on	2.4 ± 1.0	3.2 ± 0.4	2.2 ± 0.6	ns
FEV1/FVC	*off*	82 ± 8.8	82.7 ± 17.0	76.5 ± 10.8	ns
	on	82.3 ± 9.11	82 ± 14	75.8 ± 13.9	ns
PEF	*off*	437.3 ± 150.0	549.5 ± 148.6	337.2 ± 147.5	ns
	on	439.6 ± 146.7	526.0 ± 138.8	336.6 ± 146.9	ns
FVC	*off*	3.1 ± 1.0	4.0 ± 0.3	2.8 ± 0.7	ns
	on	3.2 ± 1.2	4.0 ± 0.6	3.1 ± 1.0	ns
FEV1/FVC (%)	*off*	110.6 ± 14.7	111.5 ± 25.9	102.3 ± 14.5	ns
	on	105.4 ± 21.9	110 ± 20.3	101.3 ± 18.4	ns
PEF (%)	*off*	95.4 ± 27.8	117.7 ± 43.2	72.7 ± 27.5	ns
	on	97.6 ± 26.7	112.5 ± 41.0	72.6 ± 25.8	$P = 0.048$, $\chi^2 = 6$ (corrected: $P = 0.72$)
FVC (%)	*off*	87.2 ± 17.2	103.5 ± 22.1	78.2 ± 15.8	ns
	on	87.5 ± 21.7	103.2 ± 25.2	87.6 ± 33.6	ns
FEV1 (%)	*off*	88.6 ± 18.1	109 ± 34.3	76 ± 21	$P = 0.018$, $\chi^2 = 8$ (corrected: $P = 0.27$)
	on	88 ± 19.3	108.7 ± 32.6	80.4 ± 21.9	ns

ns, not significant.

The results from the PFTs and the respiratory muscle strength assessments results for each group are shown in Table 1. L-dopa repletion did not significantly change the performance within each group of patients (*on* vs. *off* results were compared with Wilcoxon's signed-rank test within each group; $P > 0.05$).

We compared the 3 groups with Kruskal–Wallis' nonparametric test during both *on* and *off* medication, and the results were corrected with Holm-Sidak corrections for multiple comparisons in Table 1). However, there were no differences in the distributions of the PFTs observed among the groups during both *on* and *off* states.

Discussion

We investigated whether a short period of L-dopa withdrawal affects the performance of individuals with PD with and without dysphagia on PFTs and whether "swallowing-safety" profile to L-dopa correlated to lung function changes from L-dopa depletion. The three groups of individuals with PD, classified according to their dysphagia status (SI, SIon, and NSI), had previously shown different patterns of cortical and brainstem activity.[17] Here, we observed that the groups' responses on PFTs did not differ during the *on* and *off* L-dopa state. Importantly, our study showed that the swallowing-safety profile of dysphagic individuals with PD is not associated with the lung function status *on* or *off* L-dopa.

The size of the population in our study, although small, is similar to the sample sizes used in previous studies and especially studies included in the latest meta-analysis on the effects of L-dopa on PFTs.[19] The latest meta-analysis[19] on the effects of dopaminergic medication on PFTs showed that some parameters are improving with L-dopa (PEF and FCV), but not the FEV. Our observations were not in keeping with the results of this meta-analysis, given that we did not observe any change with L-dopa repletion, even though our study methodology was similar to all the studies included in the meta-analysis (i.e., duration of withdrawal, and so on), as were the number of participants included, albeit small.[19] Specifically, for the parameters of PEF% and FEV1%, comparison did not reach significance after the corrections for multiple comparisons (Holm-Sidak) took place. It is important to mention that the age and severity of symptoms in our group of patients were similar to the patients studied in the included studies in the meta-analysis.[19] From our comparisons of the acquired PFT values during the studies to the predictive values, calculated on an individual basis, we observed that our group had low agreement between the two values on the MEP, MIP, and SNIP assessments both *on* and *off* medication, and that they showed good

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agreement, but not excellent, for the remainder of parameters. Although the age and severity of symptoms were similar to the ones in the literature, not many of the PFTs recorded in our study deviated from the predicted values. We observed that MEP, MIP, and SNIP were the parameters that our group of individuals with PD showed differences in compared to the predictive values. It should be noted that although the values of these parameters were lower than predicted, they still did not correlate to dysphagia severity in individuals with PD. Maximal inspiration and expiration pressure assessments have limitations when used in a clinical population, principally their dependence on maximal voluntary neuromuscular activation, which is difficult to ascertain and they require a hermetic seal around the mouthpiece. As a consequence, low values may be owing to true muscle weakness, a submaximal effort, or air leaks in the case of facial muscle weakness, which might be the case in individuals with PD. However, of interest, the values of SNIP assessment were reduced compared to the predicted, but again there was no relationship to dysphagia in this population we studied, especially those with swallowing disorders.

Of interest, the mean LED values in our study were comparable only to one study of the four in the meta-analysis,[29] in which individuals with PD has a diagnosis for a longer duration compared to our population. In the study by De Pandis et al.,[29] the PFT parameters of FEV1 and FVC were reduced with respect to the predicted values with L-dopa. We did not observe similar behavior in our study, but it would be really interesting to evaluate whether different amounts of L-dopa could have different effects on PFTs and swallowing as well.

Moreover, it was interesting to observe that even for the cases whose swallowing function became (SIon) or remained (SI) unsafe with L-dopa, the PFTs profile did not change and did not correlate to swallowing safety. In the recent study by Monteiro et al.,[30] individuals with PD and swallowing complaints showed reduced FVC and PEF values compared to subjects with no complaints for their swallowing and controls. However, we should state that swallowing performance of the patients in the Monteiro study[30] might not have been homogeneous across the groups given that the subjective dysphagia complaints by the patients can be different compared to the results from objective swallowing assessments, such as the videofluoroscopy assessments used in our study. As a point of fact, in that study,[30] only 6 of 30 patients showed dysphagic signs on VFS.

Here, we used a swallowing-safety profile to L-dopa to group the participants, and based on the knowledge that the two sensorimotor acts, respiration and swallowing, share a common neural pathway, we expected to observe changes within and differences between the groups. However, we did not find any differences. Notably, several studies in PD failed to show differences in respiratory muscle strength assessments between controls and/or predicted values.[31,32] In our study, we also did not observe changes in these respiratory parameters with L-dopa. This suggests that respiratory muscle strength in PD may be unrelated to dopaminergic dysfunction.[33] Adding to this argument, the impaired pulmonary function is thought to be a result of a combination of: (1) poor posture restricting chest and abdominal movements; (2) rigidity resulting in poor chest wall compliance; and (3) disrupted respiratory muscle coordination.[11] This may be explained by pathology outside the basal ganglia and the involvement of nondopaminergic neurons.[34] Last, and of importance, it should be mentioned that there are no longitudinal data to show how swallowing impairments, respiration, and treatment with L-dopa evolve with disease progression. It should be noted that the two systems, respiration and swallowing, might show different patterns of severity progression and therefore the short dopaminergic withdrawal might not be adequate to reveal changes in the groups of patients.

In summary, we demonstrated that dopamine replacement after a short period of withdrawal has little impact on respiratory muscle strength assessments and PFTs on individuals with PD and no correlations between the PFTs to dysphagia *on* and *off* L-dopa. There were also no differences on PFTs found between the different groups based on their swallowing-safety profile *on* and *off* L-dopa.

Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique.

T.S.: 2B, 2C, 3A, 3B
M.L.H.: 1C, 2B, 3A
C.K.: 2C, 3B
L.B.: 2C, 3B
M.v.H.: 2C, 3B
E.M.: 1C, 2B, 2C, 3A, 3B

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. This table shows the intraclass correlations (ICCs), 95% confidence interval (CI), and the results of the ANOVA with Friedman within subjects. Please note the low agreement for SNIP, MIP, and MEP between the predicted and acquired data in the study during *off* and *on* L-dopa for all the subjects.

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