Impact of Levodopa in Lung Functions in Patients with Parkinson Disease

Medha Tandon1,2,3, Faiz M. H. Ahmad1,2,3, Subramanian Narayanan1,2,3, Charu Mohan1,2,3, Simone Yadav1,2,3
Department of 1Medicine, Army College of Medical Sciences, Departments of 2Neurology and 3Respiratory Medicine, Base Hospital, Delhi Cantt, New Delhi, India

Abstract

Background: Parkinson’s disease (PD) is the second most common neurodegenerative disorder known primarily by its motor symptomatology. These motor manifestations are also hypothesised to affect the respiratory muscular function of PD patients contributing to restrictive pattern of ventilatory dysfunction. Previous reports attempting to detect these abnormalities through spirometric assessments have been inconclusive. Attempts at reversal of the restrictive abnormalities by levodopa therapy too, have yielded conflicting results. Objectives: This study aims to classify spirometric abnormalities in asymptomatic PD patients after levodopa withdrawal and document changes after levodopa replacement. Methods: Thirty-six non-smoker PD patients without pre-existing respiratory abnormalities were enrolled. Their standard spirometric values- FEV1, FVC and FEV1/FVC, were noted before and after their morning levodopa dose. Results: Nineteen patients had abnormal PFT values at baseline - 14 restrictive and 5 obstructive defects. Fourteen patients showed improvement in their pulmonary performances after dopamine administration with 6 showing complete reversibility. Statistically significant improvement in the post-levodopa FVC values was seen in patients with restrictive disorder (P value=0.04) but not for obstructive disorders. Discussions: This pilot study characterised that 39% of PD patients had restrictive ventilatory defects prior to morning levodopa administration. Of these, 40% showed improvement after levodopa administration. Conclusion: Restrictive defects are common in PD patients which are evident on routine spirometric screening. These defects are reversible on levodopa administration.

Key Words: Levodopa, restrictive defects, spirometry

INTRODUCTION

Parkinson’s disease (PD) is the second most common neurodegenerative disorder in the world primarily affecting the older demographics. PD is characterised by degeneration of the dopaminergic neurons in the substantia nigra pars compacta of the basal ganglia leading to cardinal manifestations of tremors, bradykinesia, rigidity and gait abnormalities.

When first described by James Parkinson in 1816, motor abnormalities predominated the symptomatology, and pulmonary dysfunction as a consequence of the motor abnormalities was also recognised.

The motor dysfunction in PD maybe postulated to affect the voluntary muscular effort of these patients and can hypothetically be a contributor to respiratory or ventilator dysfunction. Despite being an important contributor of morbidity and increased hospital admissions, this issue has been rarely addressed in scientifically significant studies. Some studies reported obstructive patterns, some a restrictive pattern and still others detected no pulmonary abnormalities in the patients.

Though initially asymptomatic, pulmonary dysfunction in PD leads to a variety of symptoms in patients causing a significant decrease in the quality of life including shortness of breath, recurrent cough, sputum production, and later recurrent pneumonia.

Previous reports concerning the effects of antiparkinsonian drugs on pulmonary function have also yielded inconclusive results. Certain studies suggest including routine spirometric analysis in management of PD patients.

Aims

This study was conducted in an Indian cohort of PD patients to:
1. Ascertain the abnormality of lung functions by spirometric analysis in PD patients in a motor “off” state (prior to delayed morning dose of medications) and
2. To document the changes in the spirometric parameters after dopamine replacement therapy.

METHODOLOGY

This cross-sectional prevalence study was carried out at a North Indian tertiary care teaching hospital. Patients with PD, diagnosed as per UK Brain Bank criteria were included. Basic...
data regarding the clinical stage of disease, current medication, known comorbidities and drug use was collected. Cognitive functions of all patients were analysed using the Non-Motor Symptom Scale. Chest radiograph, echocardiograph and ECG were done to reliably rule out any structural, respiratory or cardiovascular pathology. Smokers, past and present; patients with inadequate cognitive functions; co-existing ailments and medications which might affect respiratory functions were excluded. The study subjects were either drug naïve or were seen in ‘motor off’ state defined as more than 12 hours of dopamine depletion after being instructed to omit the morning dose of medications.

Spirometry was performed according to the American Thoracic Society regulations. The pulmonary function test (PFT) included Forced expiratory volume in 1st second (FEV$_1$), Forced Vital Capacity (FVC) and the ratio between the two (FEV$_1$/FVC). The graphs and values were analysed for a valid test with adequate effort. Tests not conforming to a proper effort and procedure were repeated till an acceptable result was obtained. Patients unable to provide proper effort were excluded from the study. The reports included the complete set of pulmonary functions along with the predictive value, an interpretation of the results and the grade of obstruction, if any. ERS/ECCS$^{[10]}$ was used as a predictive reference and the normogram values were adjusted for sex, height and weight. The type of abnormality was noted and classified as mild, moderate or severe. The patients were then given their regular dose of levodopa and subjected to repeat PFT after approximately 90 minutes, when the patient reported his best “on” stage. The same patient ID was used for a posttherapy PFT and a comparison between the pre- and posttest values was obtained.

Qualitative data was expressed as frequencies and percentage. Quantitative data was expressed as Mean ± Standard Deviation (SD) and Median (minimum/maximum). Paired sample t-test was performed using SPSS software. A $P$ value < 0.05 was considered statistically significant. (Confidence Interval = 95%).

**Results**

A total of 36 IPD patients, 29 males and 5 females, were included in the study (n = 36). Their ages ranged from 45 to 80 years with a mean of 63.470 (SD = 9.002). The mean duration of the disease was 4.697 years (SD = 2.721) with a minimum of 0 years and maximum of 11 years. The mean UPDRS score was 40.697 (SD = 19.500) with a minimum score of 10 and a maximum of 76. The mean Hoen and Yahr stage for the sample population was 1.833 (SD = 0.924) with a minimum score of 1 and a maximum of 4. The mean BMI for the sample population was 24.252 (SD = 4.545) [Table 1].

**Spirometric abnormalities**

Of the 36 patients, 19 had an abnormal PFT at baseline with 14 showing a restrictive and 5 an obstructive defect. A mild restrictive pattern was seen in 11 patients and moderate restrictive in 3 patients [Graph 1].

No statistically significant correlation was seen in 11 patients and moderate restrictive in 3 patients [Graph 1].

No statistically significant correlation was present between the UPDRS staging and the baseline PFT values ($P$ value 0.659).

**Reversibility**

Subsequent data includes the 19 patients with abnormal findings. Majority of the patients (73.68%) with an abnormal PFT showed improvement in their ventilatory function subsequent to dopamine administration [Graph 2].

Patients with a restrictive disorder prior to levodopa administration showed a statistically significant improvement in their FVC values following medication ($P$ value = 0.04*).
Six patients (31.58%) also showed complete normalisation of the PFT values signifying complete reversibility of the defect. However, patients with an obstructive disorder did not show a statistically significant improvement in their PFT values ($P$ value = 0.24).

**Discussion**

First mentioned in the seminal essay by James Parkinson, respiratory difficulties have been neglected in PD despite the fact that respiratory difficulties are very common complications in PD and are responsible for recurrent admissions. In the late 1960s, Neu HC et al. studied the respiratory difficulties faced by PD patients and attempted to correlate them to the clinical features of tremors, rigidity and bradykinesia. The defect was characterised as obstructive and attributed to autonomic disturbances and increased parasympathetic tone present in PD. Obenour WH, et al. conducted their study in 1972 on 31 patients and found similar obstructive defects.

In the same year, Nakano et al. attempted to check the reversibility of the respiratory symptoms with levodopa therapy on 23 patients and found promising results.

Even though data from recent times is limited, contributions have been made to the understanding of the pulmonary abnormalities in PD by Satyaprabha et al. who in 2005, studied PFT abnormalities in 35 PD patients and concluded that forced vital capacity (FVC), maximum voluntary ventilation (MVV), maximum expiratory pressure (MEP) and maximum inspiratory pressure (MIP) were significantly reduced in patients compared to controls. They also revealed a restrictive defect which improved on subsequent levodopa administration.

A meta analysis in 2016 concluded that both obstructive and restrictive defects are seen in PD. The study further suggested that larger number of patients were needed to conclude on the benefit with levodopa. O’Callaghan et al. in their extensive review have comprehensively listed detailed and analysed all studies published till 2018 on the subject. The authors concluded that there is a dearth of studies, contradictions between the restrictive and obstructive or upper airway obstruction results. In addition, the effect of dopaminergic replacement is also contradictory.

This study included PD patients who were either treatment naïve or on levodopa and other dopaminergic therapy. These patients were subjected to PFT after omission of the morning dose of dopaminergic drugs, or in naïve state and thereafter following their usual morning dopaminergic dose. Moreover, these patients did not have clinical symptoms referable to the respiratory or cardiac systems for which they might seek medical attention.

However, a majority of our patients (53%) had ventilatory abnormalities on PFT, restrictive pattern being more common, noted in 40% of the patients. Most of these were mild restrictive defects, which is consistent with the earlier studies by Satyaprabha et al. and Sabate et al.

Restrictive patterns seen on PFTs are indicators of ventilatory dysfunction, as opposed to obstructive patterns commonly associated with airway disease. It can be postulated that the restrictive defect could be attributed to the impaired respiratory effort consequent to the motor dysfunction observed in PD and manifest as breathlessness and tachypnea. When severe, it may cause nocturnal hypoventilation which in turn may lead to impaired sleep and daytime somnolence seen in PD. This also explains the reversal of these restrictive patterns after restoration of dopaminergic status.

The obstructive pattern noted in 5 patients may be due to an underlying undiagnosed pulmonary pathology.

Since this study did not find any significant correlation between the stages of the disease characterised by the UPDRS score and the pulmonary function abnormality, it may be advisable to include PFT testing in all PD patients regardless of the stage of the disease so as to diagnose these abnormalities timely and adjust the therapy preventing further complications in the future. Only limited data was available for this parameter in the previous studies, one such being that conducted by Magdalena Sabate et al.

Traditionally known for motor manifestations, this disease has been associated with loss of dopamine producing neurons in the striatum. Replacement of dopamine by various modalities has been the cornerstone of therapy for PD, largely revolving around the daytime activities of the patient. However, often the dopamine replacement is eccentric and maybe inadequate especially at night. The possibility that there is an unaddressed nocturnal dopaminergic deficit is important. These PD patients commonly have disturbing nocturnal symptomatology. The nocturnal symptoms are likely to be worsened by all confounding variables including subclinical spirometric abnormalities. Thus, the importance of detecting and characterising ventilatory restrictive deficits reversible on levodopa supplementation as addressing this therapy deficit at any point of time, and especially at night has the potential to improve the quality of life of these patients.

To this aim, this study demonstrated significant improvements in the restrictive defect in three fourths of patients following levodopa medication. Complete reversibility was attained in 40% of the cases showing similar findings to studies by Nakano et al. and Torsney et al.

If these results are confirmed on larger studies, it may be prudent to include PFTs in the basic workup of PD patients. Further, proving the reversibility of the defects with levodopa administration will necessitate changes in the regimen for better round the clock supplementation. Since only clinical and patient-reported parameters were used to classify the patients as being in the ‘on’ or the ‘off’ state, it is recommended that these findings be confirmed by larger studies with more rigorous definitions including measuring the drug levels in the body. Also, it may be suggested that more exhaustive methods like
whole body plethysmography, ABG, and DLCO be used to validate the respiratory abnormalities in the patients in addition to the basic spirometric tests. As MIP and MEP are sensitive indicators of muscle strength and have not been studied in this research, it may also be included in larger studies conducted in the future.

In addition to having a small sample size, this study suffers from the drawback of being an observational study. Assessment of diurnal variations of levodopa levels was not attempted. Doses of dopamine agonists were not standardised for the patients as the optimisation of therapy in relation to respiratory abnormalities was not studied. However, it is one of the largest yet reported on PFT defects and their reversibility on dopamine replacement.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References
1. Parkinson J. An essay on the shaking palsy, 1817. J Neuropsychiat Clin Neurosci 2002;14:223-36.
2. Hoehn MM, Yahr MD. Parkinsonism: Onset, progression and mortality. Neurology 1967;17:427-42.
3. Gandhi S, Wood NW. Molecular pathogenesis of Parkinson’s disease. Hum Mol Genet 2005;14:2749-55.
4. Fontana GA, Pantaileo T, Lavorini F, Benvenuti F, Gangemi S. Defective motor control of coughing in Parkinson’s disease. Am J Respir Crit Care Med 1998;158:458-64.
5. Pennington S, Snell K, Lee M, Walker R. The cause of death in idiopathic Parkinson’s disease. Parkinsonism Relat Disord 2010;16:434-7.
6. Neu HC, Connolly JJ Jr, Schwertley FW, Ladwig HA, Brody AW. Obstructive respiratory dysfunction in Parkinsonian patients. Am Rev Respir Dis 1967;95:33-47.
7. Sathyaprabha TN, Kapavarapu PK, Pal PK, Thennarasu K, Raju TR. Pulmonary functions in Parkinson’s disease. Indian J Chest Dis Allied Sci 2005;47:251-7.
8. Sabate M, Rodriguez M, Mendez E, Enriquez E, Gonzalez I. Obstructive and restrictive pulmonary dysfunction increases disability in Parkinson disease. Arch Phys Med Rehabil 1996;77:29-34.
9. Lee MA, Prentice WM, Hildreth AJ, Walker RW. Measuring symptom load in idiopathic Parkinson’s disease. Parkinsonism Relat Disord 2007;13:284-9.
10. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. Eur Respir J 1993;6(Suppl 16):S5-40.
11. O’Callaghan A, Walker R. A Review of pulmonary function in Parkinson’s disease. Journal of Parkinsonism and Restless Legs Syndrome 2018;8:13-23.
12. Obenour WH, Stevens PM, Cohen AA, McCutchen JJ. The causes of abnormal pulmonary function in Parkinson’s disease. Am Rev Respir Dis 1972;105:382-7.
13. Nakano KK, Bass H, Tyler HR. Levodopa in Parkinson’s disease: Effect on pulmonary functions. Arch Intern Med 1972;130:346-8.
14. Johnson JD, Theurer WM. A stepwise approach to the interpretation of pulmonary function tests. Am Fam Physician 2014;89:359-66.
15. Polkey MI, Green M, Moxham J. Measurement of respiratory muscle strength. Thorax 1995;50:1131-5.
16. Torsney KM, Forsyth D. Respiratory dysfunction in Parkinson’s disease. J R Coll Physicians Edinb 2017;47:35-9.