

Respiratory Dysfunction in Parkinson's Disease: Relation with Dysautonomia

Meghashree Sampath, Geetanjali Bade, Vinay Goyal¹, Achal K. Srivastava¹, Ashok K. Jaryal, Kishore K. Deepak, Anjana Talwar

Departments of Physiology and ¹Neurology, All India Institute of Medical Sciences (AIIMS), New Delhi, India

Abstract

Background: Parkinson's disease (PD) is a neurodegenerative disease perceived as a motor disorder. It is most commonly associated with autonomic dysfunction, affecting multiple systems. This altered autonomic control might be reflected by a parallel change in the airway caliber of these patients. **Aim:** To correlate the pulmonary impairment in patients with Parkinson's disease with the underlying dysautonomia. **Materials and Methods:** A total of 30 patients with Parkinson's disease participated in the study. Heart rate (HR) variability was recorded for 5 min to assess the autonomic dysfunction, followed by impulse oscillometry (IOS) and spirometry. IOS being an effort independent technique uses sound waves at different frequencies (5–25 Hz) to measure the airway impedance. **Results:** There was a significant decrease in SDSD (6.60 (10.18–6.01) vs. 12.22 (13.95–11.30); $P = 0.04$), RMSSD (6.59 (10.17–5.50) vs. 12.20 (13.93–11.28); $P = 0.04$), and total power (315.8 (506.3–120.7) vs. 771.3 (799.0–643.6); $P = 0.04$) in stage II as compared to stage I. Resistance at 20 Hz (R20) was found to be positively correlated with SDSD ($r = 0.40$, $P = 0.04$), RMSSD ($r = 0.40$, $P = 0.04$), and HF ($r = 0.41$, $P = 0.03$). **Conclusion:** Amongst the PD population, any changes in the parasympathetic component (responsible for bronchoconstriction) due to the underlying dysautonomia might be reflected as increased airway resistance in the pulmonary system.

Keywords: Autonomic dysfunction, heart rate variability, impulse Oscillometry, Parkinson's disease, pulmonary impairment

INTRODUCTION

Parkinson's disease (PD) is the most common neurodegenerative disorder perceived as a disease of the motor system.^[1] Though nonmotor manifestations of PD are now receiving increased attention, the diagnosis of the condition is still based on the motor signs (such as rigidity, akinesia, and resting tremors).

Autonomic nervous system (ANS) dysfunction is common in PD, affecting 70%–80% of patients and causing significant morbidity and discomfort. As proposed by Braak, the alpha synuclein deposition and neurodegeneration in respiratory-related neurons in the pons and medulla oblongata have a detrimental impact on respiration,^[2] involving impaired ventilation, weakness of respiratory muscles, leading to hypophonia and swallowing disorders.^[2–4]

The dysautonomia in these patients results in affecting other systems as well as reported in the gastrointestinal system, cardiovascular system, sexual behavior, and bladder function.^[5] However, any impairment in pulmonary function has not been clinically manifested due to the sedentary lifestyle of the patients though many studies have been reported that have used an effort-dependent technique (Spirometry) to assess pulmonary function and have observed changes in lung volumes in these patients such as airflow limitation, restrictive pattern or mixed pattern, upper airway dysfunction, and diminished strength of respiratory muscles.^[6–10]

Breathing involves a complex interaction between the central autonomic network (CAN) and respiratory neuron network (RNN).^[11] Both RNN and CAN interact harmoniously

to regulate the contraction of respiratory muscle, ensuring that normal blood gas levels are maintained during speech, volitional breathing, and ventilatory load. Additionally, dispersed network of the forebrain region may regulate the influences on baroreflex and chemoreflex via reciprocal projections within the brainstem and exert modulatory influences on cardiovascular autonomic function.^[12]

Even though obstructive patterns have been observed in patients with Parkinson's disease, it is not clear whether it is due to the weakness of musculoskeletal elements or due to changes in the airway resistance or both. To the best of our knowledge, any association of airway resistance with heart rate variability (HRV) has not been reported in patients with Parkinson's disease. Therefore, we postulate that the abnormality in the autonomic tone in PD patients might be reflected by a parallel change in the airway caliber.

Address for correspondence: Dr. Anjana Talwar,
Department of Physiology, All India Institute of Medical Sciences,
New-Delhi - 110 029, India.
E-mail: anjanatalwar@gmail.com

Submitted: 25-Oct-2021 Accepted: 03-Feb-2022 Published: 06-Apr-2022

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DOI: 10.4103/aian.aian_940_21

METHODS

Study design

This was an observational cross-sectional study assessing the correlation of dysautonomia in PD with respiratory impedance. Patients were selected based on inclusion and exclusion criteria after clinical diagnosis from neurology outpatient department from a tertiary care hospital. The study protocol was approved by the Institute Ethics committee (Ref no: RT-3/22.07.2015). A written informed consent was taken from all the patients.

Participants

Thirty patients with Parkinson's disease participated in the study. PD was diagnosed according to the United Kingdom brain bank criteria.^[13] Clinically diagnosed PD patients having H-Y stage from I to IV, both male and female with ages ranging from 40 to 70 years were included in the study. All patients were nonsmokers. Patients with a history of lung or cardiovascular disease affecting pulmonary function and those unable to perform pulmonary function test (PFT) due to anatomical abnormalities were excluded. Patients on any medication affecting sympathetic/parasympathetic nervous system were noted. Demographic features such as age, sex, height, and weight were noted. Disease characteristics like time since onset of symptoms and severity (evaluated by Hoehn-Yahr scale) were recorded. The patients were divided into two groups based on the Hoehn-Yahr scale (stage I and stage II) [Table 1].

Study procedure

The patients were made to rest in the supine position for 15 min after taking a brief history, and heart rate variability (HRV) was recorded (Lead II ECG) for 5 min. PFT was performed using spirometry (Medisoft Spiroair) and impulse oscillometry system (IOS-Jaeger). HRV measurement was followed by IOS and spirometry with a break of 5 min after each session on the same day. The patients were asked to wear loose and comfortable clothing and also to avoid food preceding 2 h of testing. Room temperature was maintained at 24°C, and the patients were instructed to close their eyes and to avoid talking, moving, coughing, or sleeping during HRV recording. Lead II ECG was recorded using the bio-potential amplifier with help of shielded cables and disposable Ag-AgCl electrodes. Sampling rates for acquiring ECG signals were 200 Hz with a scaling of 100 mmHg/V.

	Patients		
	Total patients n=25	Stage I n=7	Stage II n=7
Severity of PD	H-Y Stage I, II, III, IV	H-Y Stage I	H-Y Stage II
Age (yrs)	60.1±9.45	55.2±8.15	59.71±9.89
Height (cm)	164.5±6.80	166±3.91	163±5.85
Weight (kg)	64.3±12.2	67±14.3	60.57±11.70
BMI (Kg/m ²)	23.5±3.93	24.40±5.39	22.48±3.73

Data has been represented as mean±SD

For the pulmonary function test (PFT), the patients were given instructions and demonstrations before the test. Trial sessions were held to get familiarized with the instrument. Volume and pressure calibration for Spirometry and IOS was performed using a 3-L syringe and a known resistance of 0.2 kPa/L/s, respectively.

Heart rate variability

As per the guidelines of Task Force (1996) at least 5 min of ECG was recorded to quantify sympathetic and parasympathetic tone. HRV was calculated from the recorded ECG using Labchart Pro 7[®] and nevrokard software. ECG signals were continuously amplified, digitized, and stored in the computer for analysis. The R-wave was detected by the software and was plotted against time. Analysis of time-domain parameters included Standard deviation of differences between adjacent NN intervals (SDSD) and The square root of the mean of the sum of the squares of differences between adjacent NN intervals (RMSSD), which primarily reflects parasympathetic activity. Frequency domain parameters were analyzed by Fast Fourier Transform (FFT) and included Low Frequency (LF, 0.04–0.15 Hz), High Frequency (HF, 0.15–0.4 Hz), and Total Power (TP, 0–0.4 Hz). Low Frequency corresponds mainly to sympathetic along with some contribution of parasympathetic activity, High Frequency corresponds to parasympathetic activity, and Total Power expresses the magnitude of the HRV in a global manner.

Impulse oscillometry

IOS is a noninvasive and effort-independent technique. After the explanation of the procedure, the patients were asked to sit comfortably without legs crossed and with a nose clip. They were asked to support their cheeks with hands to prevent shunting of impulses, followed by normal tidal breathing in a relaxed state for at least 30–45 s during which around 120–150 sound impulses/pressure oscillations were pushed into the lungs from which different parameters were calculated. Oscillating sound waves of frequencies ranging between 5 Hz and 35 Hz generated by an external loudspeaker travel superimposed upon the normal tidal breathing through the large and small airways. Lower frequencies (<15 Hz) travel deeper into the lung and distal airways, whereas higher frequencies (>20 Hz) die off at proximal or large airways. Resistance and Reactance at 5 Hz and 20 Hz are denoted as R5, R20, and X5, X20, respectively. Therefore, resistance at lower frequency i.e., 5 Hz (R5) gives information about the total respiratory system, and resistance at higher frequency i.e., 20 Hz (R20) provides information about central airways, and the difference between R5 and R20 (R5-R20) reflects peripheral/small airways.^[14] Resistance is the in-phase component of respiratory impedance that reflects forward pressure of conducting airways, whereas reactance is the out of phase component reflecting capacitive and inductive properties of airways.^[15] Coherence has a value between 0 and 1 reflecting reproducibility of measurements and for accurate testing coherence at 5 Hz should be >0.8 cm H₂O and at 20 Hz coherence should be between (0.9 and 1).^[14] An average of 3–4 technically acceptable recordings were taken for calculations.

Software for signal analysis

Offline analysis of ECG signals was done using signal acquisition and analysis software Labchart Pro 7® (AD instruments, Australia) nevrokard software. IOS and Spirometry parameters were analyzed using JLAB and Medisoft software, respectively, installed in the instrument provided by the manufacturer.

Statistical analysis

Each parameter was tested for distribution of the data based on standard normality tests (D'Agostino-Pearson omnibus normality test and Shapiro-Wilk test). Dependent variables were parameters of HRV and parameters of IOS. Two group comparisons were done using unpaired t-test and Mann-Whitney U test, as appropriate. To study the relationship between HRV and IOS techniques, Pearson's correlation was used. The level of statistical significance was set at $P < 0.05$. All statistical analyses were performed using GraphPad Prism version 5.00 for Windows (GraphPad Software, Inc., USA).

RESULTS

Overall 30 patients with Parkinson's disease participated in the study [Table 1]. All patients were on medication during the recording. The data of 25 patients were analyzed after removing artifacts. The data were stratified based on disease severity. There was a significant decrease in SDDSD ($P = 0.04$), RMSSD ($P = 0.04$), and total power (0.04), and an increase in parameters of IOS (data published elsewhere) in stage II as compared to stage I [Table 2]. Resistance at 20 Hz (R20) was found to be positively correlated with SDDSD ($P = 0.04$), RMSSD ($P = 0.04$), and HF ($P = 0.03$) [Table 3].

DISCUSSION

In the present study, we found a significant decrease in total power encompassing very low frequency, low frequency, and high frequency. Our results are in accordance with the other authors who have reported similar findings with a decrease in total power or decrease in all spectral bands^[7,17] in the group with higher H-Y in comparison with the group with a lower H-Y stage. Harnod *et al.*,^[18] reported a significant change in HRV parameters only with disease duration and not with severity of the disease because in this particular study, groups were divided according to the severity assessed by Unified Parkinson's Disease Rating Scale (UPDRS) and not H-Y staging which is used in the present study.

The short-term HRV examination is sufficiently sensitive for evaluation of the progression of autonomic dysfunction in PD. The lower cardiac autonomic tone has been attributed to either central or peripheral autonomic regulatory impairment, with the presence of Lewy bodies in the dorsal motor nucleus of vagus as well as sympathetic and parasympathetic ganglion.^[2]

On assessing the pulmonary function, we found a significant increase in the total impedance of the system with increasing severity of the disease, but there was no change in Spirometric

Table 2: Parameters of HRV and IOS in stage I and stage II

	Stage I (n=7)	Stage II (n=7)	P
SDDSD (ms)	12.22 (13.95-11.30)	6.60 (10.18-6.01)	0.04*
RMSSD (ms)	12.20 (13.93-11.28)	6.59 (10.17-5.50)	0.04*
TP (ms)	771.3 (799.0-643.6)	315.8 (506.3-120.7)	0.04*
LF (ms)	106.7 (357.3-62.20)	83.40 (137.5-19.31)	0.12
HF (ms)	76.06 (101.7-16.95)	29.05 (32.43-12.01)	0.16
R5# (kPa/l/s)	0.32 (0.36-0.28)	0.47 (0.60—v0.36)	0.04*
X5# (kPa/l/s)	-0.13 (-0.10)-(-0.16)	-0.13 (-0.11)-(-0.29)	0.94
R20# (kPa/l/s)	0.25 (0.28-0.20)	0.30 (0.40-0.25)	0.04*
Ax# (kPa/l)	0.67 (0.84-0.22)	0.66 (2.50-0.41)	0.70
Fres# (Hz)	17.27 (19.49-16.10)	17.41 (24.04-16.39)	0.43
Z5# (kPa/l/s)	0.35 (0.38-0.32)	0.49 (0.66-0.38)	0.07

Data have been represented as median (interquartile range). The level of significance is denoted by an asterisk (*) at 5%. # published data^[16]

Table 3: Correlation of HRV and IOS parameters in PD patients (n=25)

	R5 (kPa/l/s)	R20 (kPa/l/s)	X5 (kPa/l/s)	Ax (kPa/l)	Fres (Hz)
SDDSD (ms)	0.27	0.40*	-0.14	0.034	-0.222
RMSSD (ms)	0.27	0.40*	-0.14	0.035	-0.221
TP (ms)	0.07	0.19	-0.15	-0.09	-0.23
LF (ms)	0.05	0.15	-0.18	-0.06	-0.21
HF (ms)	0.21	0.41*	0.02	-0.13	-0.13

Level of significance is denoted by asterisk (*) at 5%.

indices.^[16] To the best of our knowledge, this has been the first study to report changes in airway impedance with disease progression in PD. However, increased airway resistance as measured by body plethysmography has been reported earlier.^[19] Previous studies have also observed reductions in lung volumes with obstructive, specifically upper airway obstruction^[6,7] and/or restrictive patterns, indicating compromised ventilation.^[1,20] This pulmonary dysfunction is aggravated by the bradykinetic disorganization of movements of respiratory-related muscles, rigidity of chest wall, damaged airway, and muscle weakness leading to decreased pulmonary compliance and increased resistance to airflow.^[19,21-23]

As was speculated by authors that the pulmonary dysfunction in PD patients might be due to the involvement of the autonomic nervous system, predominantly increase in parasympathetic activity.^[24] In accordance with that, we found a positive correlation of R20 (Resistance at 20 Hz) i.e., proximal resistance with SDDSD, RMSSD, HF (reflecting parasympathetic activity).

The variability of heart rate is generally assessed by examining the distributions in the temporal and frequency domains.^[25] Those oscillations that take place at respiratory frequency are the main component of spontaneous variability in heart rate called as respiratory sinus arrhythmia (RSA).^[26] Due to this RSA, the power spectral density has a peak at respiratory frequency, referred to as the "high-frequency component of the

power spectral density (range 0.15 to 0.4 Hz).²⁷ There exists a reciprocally coupled relationship between the cardiovascular and respiratory systems, this mutual coupling results in an increase in the variability of the oscillator's frequencies allowing them to adapt and respond to external perturbations as well as to evolve complex patterns of activity.²⁸

Changes in respiratory rate or tidal volume lead to changes in the RSA magnitude i.e., an increase in the respiratory volume and/or cycle results in an increase in the RSA amplitude independently of vagal tone²⁹⁻³¹ which would eventually be reflected in the high-frequency component of HRV when measured.

Based on the relevant literature, there are two possible mechanisms at play. The direct pathway (central mechanism) that mediates the activation or inactivation of neurons in cardioinhibitory center which reflects the spreading of neural activity from the respiratory to the cardio-inhibitory centers.³² Also, during breathing various respiratory and cardiovascular parameters like venous return, intrathoracic pressure, pH, systemic blood pressure, partial pressure of blood gases – pCO₂ and pO₂, etc., oscillate at the rhythm of breathing,³³ and these oscillations have a great potential to relay to RSA via reflex mechanism creating indirect pathways (*peripheral mechanisms of RSA*).^{31,32} Animal models of PD have also reported pulmonary dysfunction attributing to both central and peripheral processes, including neurodegeneration of respiratory-related neurons and abnormal accumulation of collagen in the alveolar septum and airways.³⁴

As described, the core symptoms of PD patients include rigidity and bradykinesia that results in slow, inflexible, gawky, and unco-ordinated movements, which weakens the tone, contractility, and co-ordination of thoracic musculature. As a consequence of which, the respiratory mechanics and pulmonary function are affected. Now this decrease in the force of the respiratory muscle and/or increase in the resistance of the airways may lead to an increase in compensation of central respiratory driving force to maintain sufficient physiological ventilation,³⁵ which might be seen to be reflected in the positive correlation of proximal resistance with parasympathetic components of HRV.

Though the variability in the heart rate of PD patients is lowered to a large extent as compared to their age-matched healthy controls. Nevertheless, as suggested by the data, we could say that amongst the PD population, any alteration in the parasympathetic domain (i.e. responsible for bronchoconstriction) due to dysautonomia might be reflected in the airway caliber of these patients.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

- Baille G, Perez T, Devos D, Deken V, Defebvre L, Moreau C. Early occurrence of inspiratory muscle weakness in Parkinson's disease. *PLoS One* 2018;13:e0190400.
- Braak H, Del Tredici K, Rüb U, de Vos RA, Jansen Steur EN, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol Aging* 2003;24:197-211.
- Troche MS, Huebner I, Rosenbek JC, Okun MS, Sapienza CM. Respiratory-swallowing coordination and swallowing safety in patients with Parkinson's disease. *Dysphagia* 2011;26:218-24.
- Hammer MJ. Aerodynamic assessment of phonatory onset in Parkinson's disease: Evidence of decreased scaling of laryngeal and respiratory control. *J Park Dis* 2013;3:173-9.
- Zesiewicz TA, Baker MJ, Wahba M, Hauser RA. Autonomic nervous system dysfunction in Parkinson's disease. *Curr Treat Options Neurol* 2003;5:149-60.
- Izquierdo-Alonso JL, Jiménez-Jiménez FJ, Cabrera-Valdivia F, Mansilla-Lesmes M. Airway dysfunction in patients with Parkinson's disease. *Lung* 1994;172:47-55.
- Sabaté M, González I, Ruperez F, Rodríguez M. Obstructive and restrictive pulmonary dysfunctions in Parkinson's disease. *J Neurol Sci* 1996;138:114-9.
- Cardoso SR, Pereira JS. [Analysis of breathing function in Parkinson's disease]. *Arq Neuropsiquiatr* 2002;60:91-5.
- De Pandis MF, Starace A, Stefanelli F, Marruzzo P, Meoli I, De Simone G, *et al.* Modification of respiratory function parameters in patients with severe Parkinson's disease. *Neurol Sci* 2002;23(Suppl 2):S69-70.
- Pal PK, Sathyaprabha TN, Tuhina P, Thenmarasu K. Pattern of subclinical pulmonary dysfunctions in Parkinson's disease and the effect of levodopa. *Mov Disord* 2007;22:420-4.
- Yu L, De Mazancourt M, Hess A, Ashadi FR, Klein I, Mal H, *et al.* Functional connectivity and information flow of the respiratory neural network in chronic obstructive pulmonary disease. *Hum Brain Mapp* 2016;37:2736-54.
- Benarroch EE. The central autonomic network: Functional organization, dysfunction, and perspective. *Mayo Clin Proc* 1993;68:988-1001.
- Gibb WR, Lees AJ. The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1988;51:745-52.
- Brashier B, Salvi S. Measuring lung function using sound waves: Role of the forced oscillation technique and impulse oscillometry system. *Breathe* 2015;11:57-65.
- Bickel S, Popler J, Lesnick B, Eid N. Impulse oscillometry: Interpretation and practical applications. *Chest* 2014;146:841-7.
- Sampath M, Srivastava AK, Goyal V, Jaryal AK, Deepak KK, Talwar A. Effect of disease severity on respiratory impedance in Parkinson's disease. *Ann Neurosci* 2020;27:63-6.
- Rodríguez M, Sabaté M, Troncoso E. Time and frequency domain analysis for the assessment of heart autonomic control in Parkinson's disease. *J Neural Transm Vienna Austria* 1996 1996;103:447-54.
- Harnod D, Wen S-H, Chen S-Y, Harnod T. The association of heart rate variability with Parkinsonian motor symptom duration. *Yonsei Med J* 2014;55:1297-302.
- Vincken WG, Darauay CM, Cosio MG. Reversibility of upper airway obstruction after levodopa therapy in Parkinson's disease. *Chest* 1989;96:210-2.
- Owolabi L, Nagoda M, Babashani M. Pulmonary function tests in patients with Parkinson's disease: A case-control study. *Niger J Clin Pract* 2016;19:66-70.
- Polatli M, Akyol A, Cildag O, Bayülkem K. Pulmonary function tests in Parkinson's disease. *Eur J Neurol* 2001;8:341-5.
- Huber JE, Darling M, Francis EJ, Zhang D. Impact of typical aging and

- Parkinson's disease on the relationship among breath pausing, syntax, and punctuation. *Am J Speech Lang Pathol* 2012;21:368-79.
23. Monteiro L, Souza-Machado A, Pinho P, Sampaio M, Nóbrega AC, Melo A. Swallowing impairment and pulmonary dysfunction in Parkinson's disease: The silent threats. *J Neurol Sci* 2014;339:149-52.
 24. Sathyaprabha TN, Kapavarapu PK, Pal PK, Thennarasu K, Raju TR. Pulmonary functions in Parkinson's disease. *Indian J Chest Dis* 2005;47:251-7.
 25. Stys A, Stys T. Current clinical applications of heart rate variability. *Clin Cardiol* 1998;21:719-24.
 26. Krohova J, Czipelova B, Turianikova Z, Lazarova Z, Wiszt R, Javorka M, *et al.* Information domain analysis of respiratory sinus arrhythmia mechanisms. *Physiol Res* 2018;67(Suppl 4):S611-8.
 27. Dick TE, Hsieh Y-H, Dhingra RR, Baekey DM, Galán RF, Wehrwein E, *et al.* Cardiorespiratory coupling: Common rhythms in cardiac, sympathetic, and respiratory activities. *Prog Brain Res* 2014;209:191-205.
 28. Winfree AT. Circadian rhythms in general. *Interdisciplinary Applied Mathematics. The Geometry of Biological Time*, 2, Springer, New York, 2001, XXVI, 779.
 29. Elghozi JL, Laude D, Girard A. Effects of respiration on blood pressure and heart rate variability in humans. *Clin Exp Pharmacol Physiol* 1991;18:735-42.
 30. Schmitz JM, Claus D, Neundörfer B, Handwerker HO. Comparison of different algorithms for evaluation of respiratory sinus arrhythmia: Cross-correlation function histogram analysis and regression analysis. *Physiol Res* 1995;44:197-203.
 31. Larsen PD, Tzeng YC, Sin PY, Galletly DC. Respiratory sinus arrhythmia in conscious humans during spontaneous respiration. *Respir Physiol Neurobiol* 2010;174:111-8.
 32. Mortola JP, Marghescu D, Siegrist-Johnstone R. Thinking about breathing: Effects on respiratory sinus arrhythmia. *Respir Physiol Neurobiol* 2016;223:28-36.
 33. Saul JP, Berger RD, Albrecht P, Stein SP, Chen MH, Cohen RJ. Transfer function analysis of the circulation: Unique insights into cardiovascular regulation. *Am J Physiol* 1991;261:H1231-45.
 34. Oliveira LM, Oliveira MA, Moriya HT, Moreira TS, Takakura AC. Respiratory disturbances in a mouse model of Parkinson's disease. *Exp Physiol* 2019;104:729-39.
 35. Zhang W, Zhang L, Zhou N, Huang E, Li Q, Wang T, *et al.* Dysregulation of respiratory center drive (P0.1) and muscle strength in patients with early stage idiopathic Parkinson's disease. *Front Neurol* 2019;10:724.