



Abnormal Pulmonary Function in Early Parkinson's Disease: A Preliminary Prospective Observational Study

Chenxi Zhang¹ · Jia Deng¹ · Yi Li¹ · Guangyu Niu¹ · Mingna Li¹ · Bin Zhang¹ · Jianjun Wang¹ · Yanling Liu² · Boyan Fang³ · Jianing Xi¹ · Hongying Jiang¹ · Zhanqi Zhao^{4,5} 

Received: 30 January 2022 / Accepted: 27 March 2022 / Published online: 25 April 2022
© The Author(s), under exclusive licence to Springer Science+Business Media, LLC, part of Springer Nature 2022

Abstract

Early Parkinson's disease (PD) may cause respiratory dysfunction; however the findings vary among studies. The aim of the preliminary prospective observational study was to explore the deterioration of pulmonary function at various stages in patients with early PD. A total of 237 patients with PD were screened. Fifty-six patients were included (modified Hoehn and Yahr stage ≤ 2.5). In addition, 56 age-matched healthy controls were also included in the study. Significant differences between the PD and control groups were found in all the investigated lung-function parameters. The maximal voluntary ventilation (MVV) percent predicted was the only parameter that distinguished PD stages ($101.1 \pm 14.9\%$ vs. $82.8 \pm 19.2\%$ vs. $71.4 \pm 12.9\%$, Hoehn and Yahr stages 1.5 vs. 2 vs. 2.5, respectively; $p < 0.005$). MVV could be the most sensitive parameter for distinguishing the severity of early-stage PD.

Keywords Early Parkinson's disease · Respiratory dysfunction · Maximal voluntary ventilation · Pulmonary function testing

Introduction

Parkinson's disease (PD) is a progressive extrapyramidal motor disorder characterized by worsening disability and immobility. While the most prevalent symptoms of PD

Chenxi Zhang and Jia Deng have contributed equally to the study.

✉ Hongying Jiang
6jhy@163.com

✉ Zhanqi Zhao
zhanqi.zhao@hs-furtwangen.de

Chenxi Zhang
bjkfyycx@163.com

Jia Deng
djlml1028@126.com

Yi Li
liyi_0301@126.com

Guangyu Niu
1245417228@qq.com

Mingna Li
152717841@qq.com

Bin Zhang
zbgzjz@sina.com

Jianjun Wang
wj999315@163.com

Yanling Liu
380425859@qq.com

Boyan Fang
fangboyanv@ccmu.edu.cn

Jianing Xi
xijn888@sina.com

- ¹ Department of Respiratory Rehabilitation Center, Beijing Rehabilitation Hospital of Capital Medical University, Xixiazhuang, Badachu, Shijingshan, Beijing 100114, China
- ² Department of Cardiovascular Rehabilitation Center, Beijing Rehabilitation Hospital of Capital Medical University, Beijing, China
- ³ Parkinson Medical Center, Beijing Rehabilitation Hospital, Capital Medical University, Beijing, China
- ⁴ Department of Biomedical Engineering, Fourth Military Medical University, Xi'an 710000, China
- ⁵ Institute of Technical Medicine, Furtwangen University, Villingen-Schwenningen, Germany

are motor function impairments, non-motor dysfunctions may present prior to motor impairment [1, 2]. PD-related respiratory dysfunction was observed as early as in 1817 [3]. However, Storch et al. found that non-motor symptoms are heterogeneous and complex and do not correlate with patients' demographic and/or motor functions [4]. Although this study did not investigate pulmonary function, various researches have reported heterogeneous pulmonary function in patients with PD. In a recent systematic review, the authors investigated 18 studies that assessed pulmonary function in PD patients [5]. Obstructive dysfunctions were identified in eight studies and restrictive dysfunctions were identified in six studies. These dysfunctions overlapped in one study. Moreover, five studies did not report any deterioration compared to either healthy control group or predicted values. Especially in early PD, it seems that only a reduction in respiratory muscle strength was observed and again the results regarding pulmonary function were contradictory [6, 7]. This study aimed to explore the deterioration of pulmonary function in early PD at various stages.

Methods

This preliminary prospective observational study was approved by the Ethics Committee of Beijing Rehabilitation Hospital, Capital Medical University (No. 2019bkky-001). Consecutive patients diagnosed with idiopathic PD between January and November 2020 were screened for eligibility. This single-center study was conducted at the Neurological Rehabilitation Center, Beijing Rehabilitation Hospital. Written informed consent was obtained from all patients prior to the study.

The inclusion criteria were as follows: patients with (1) idiopathic PD diagnosed by a neurologist according to the Movement Disorder Society criteria [8] with modified Hoehn and Yahr (H&Y) stage ≤ 2.5 [9]; (2) stable vital signs, with no serious cardiopulmonary disease (such as chronic obstructive pulmonary diseases, bronchial asthma, and heart failure). Nucleic acid screening, blood tests and chest CT were performed to rule out the possibility of COVID-19 and other pulmonary diseases (3) stable medication status, with no drug adjustments within 3 months; (4) comorbidities did not require special in-hospital treatment; (5) absence of deep brain stimulation therapy or in vivo implantation treatment; (6) the ability to sit unsupported and complete the examination; and (7) the ability to completely understand and willingly sign the informed consent form. Patients who met any of the following criteria were excluded: (1) active smokers or those who quit smoking ≤ 5 years prior; (2) diagnosed with pulmonary diseases including active pulmonary disease within 1 month of the study; (3) inability to provide proper effort during

pulmonary function tests; (4) a Clinical Dementia Rating [10] score > 0.5 ; or (5) a hearing impairment.

After oral administration of drugs for PD, pulmonary function test was performed by trained and qualified personnel using standardized equipment according to the guidelines [11, 12]. All tests were performed at the same time of the day, in the morning hours (09:00–12:00 am), to minimize possible diurnal variation. Forced vital capacity (FVC), forced expiratory volume in 1 s (FEV₁), peak expiratory flow (PEF) and maximal voluntary ventilation (MVV) were measured by spirometry, whereas total lung capacity (TLC), residual volume (RV), diffusing capacity of the lungs for carbon monoxide (DLCO) were measured using the single-breath method (MasterScreen-PFT, Jaeger, Höchberg, Germany). The predicted value for MVV (MVV%Pred) was determined based on previous studies [13]. Other predicted values were calculated using the European Community of Coal and Steel prediction equations [14]. Maximal inspiratory pressure (MIP) was measured using a hand-held mouth pressure meter (POWERbreathe KH2, HaB Ltd., UK). The MIP was expressed as a percentage of the predicted values introduced in a previous study [15].

The sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) was applied to assess non-motor and motor experiences of daily living and motor complications [16].

Age-matched healthy controls were included in the study. They were healthy at the time of the study and were screened for the same exclusion criteria as the PD patients.

Statistical analyses were performed using MATLAB R2015a (MathWorks, Inc., Natick, USA). The Lilliefors test was used to test for normality. For normally distributed data, the results are expressed as mean \pm standard deviation. A paired *t* test was used to compare the healthy controls and patients with early PD. One-way ANOVA was used to compare the pulmonary function parameters at various PD stages. The chi-square test with Yates correction was used for categorical variables where applicable. A *p* value < 0.05 was considered statistically significant. The Holm–Bonferroni method was used to adjust the significance levels for multiple comparisons.

Results

A total of 237 PD patients were screened and finally 56 early PD patients were included. In addition, 56 age-matched healthy controls were included. Table 1 compares the demographic and pulmonary function parameters between the PD and control groups. Significant differences were found in all the investigated parameters. Further comparisons were conducted for pulmonary function parameters at various PD stages (Fig. 1). FEV1%pred began to decrease at H&Y Stage

Table 1 Comparison of demographics and pulmonary function parameters between the Parkinson's disease and control groups

	Healthy N=56	PD N=56	P*	H&Y 1.5 N=5	H&Y 2.0 N=36	H&Y 2.5 N=15	P [#]
Age (yrs)	60.2±8.2	59.9±8.6	0.82	51.8±11.0	61.0±6.8	59.7±10.7	0.13
Height (cm)	165.3±7.3	165.6±7.5	0.88	165.4±6.4	164.7±7.8	167.7±7.0	0.58
Weight (kg)	66.8±10.7	65.3±8.9	0.43	67.4±5.8	65.6±9.3	64.1±9.0	0.83
Gender (m:f)	24:32	30:26	0.34	4:1	17:19	9:6	0.32
PD duration (yrs)	n.a.	7.2±4.6		4.8±3.7	7.0±4.8	7.4±4.9	
FEV ₁ %pred	102.5±11.3	93.5±15.0	<0.001*	95.6±7.7	96.5±13.5	85.7±17.7	<0.001 [#]
FVC %pred	104.4±11.3	97.9±15.5	0.01	96.1±8.1	101.8±13.8	88.5±18.4	<0.001 [#]
FEV ₁ /FVC	0.81±0.05	0.78±0.06	0.006*	0.82±0.06	0.78±0.04	0.78±0.05	0.04
PEF %pred	99.8±14.2	81.9±21.2	<0.001*	97.4±11.1	82.4±20.9	75.4±22.5	<0.001 [#]
RV %pred	111.3±22.2	64.5±30.9	<0.001*	67.5±21.1	61.0±31.1	72.0±33.1	<0.001 [#]
TLC %pred	95.7±10.4	81.8±17.7	<0.001*	85.0±12.0	82.1±19.2	80.0±16.3	<0.001 [#]
MVV %pred	97.8±14.0	80.9±19.2	<0.001*	101.1±14.9	82.8±19.2	71.4±12.9	<0.001 [#]
DLCO %pred	86.9±12.8	77.4±22.5	0.007*	71.9±15.0	75.6±26.1	83.3±13.1	0.03

yrs years; %pred percent predicted; FEV₁ forced expiratory volume during the first second; FVC forced vital capacity; PEF peak expiratory flow; RV residual volume; TLC total lung capacity; MVV maximal voluntary ventilation; DLCO diffusing capacity of the lung for carbon monoxide; PD Parkinson's disease; H&Y Hoehn&Yahr stages

*Significantly different between healthy and PD groups after post-hoc adjustment

[#]Significantly different among healthy and 3 H&Y stages after post-hoc adjustment

2.5. PEF %pred started to decrease at Stage 2. Early PD (even started from stage 1.5) showed a significant drop of RV %pred but the values were similar among studied H&Y stages. MVV percent predicted was the only parameter that distinguished PD stages after adjusting for significance levels for multiple comparisons. MIP %pred was 77.8±18.5, 62.8±44.7 and 56.7±29.5 for H&Y stages 1.5, 2 and 2.5, respectively. The MDS-UPDRS score was 10.8±4.5, 27.3±8.2, and 37.3±12.9 for H&Y stages 1.5, 2 and 2.5, respectively.

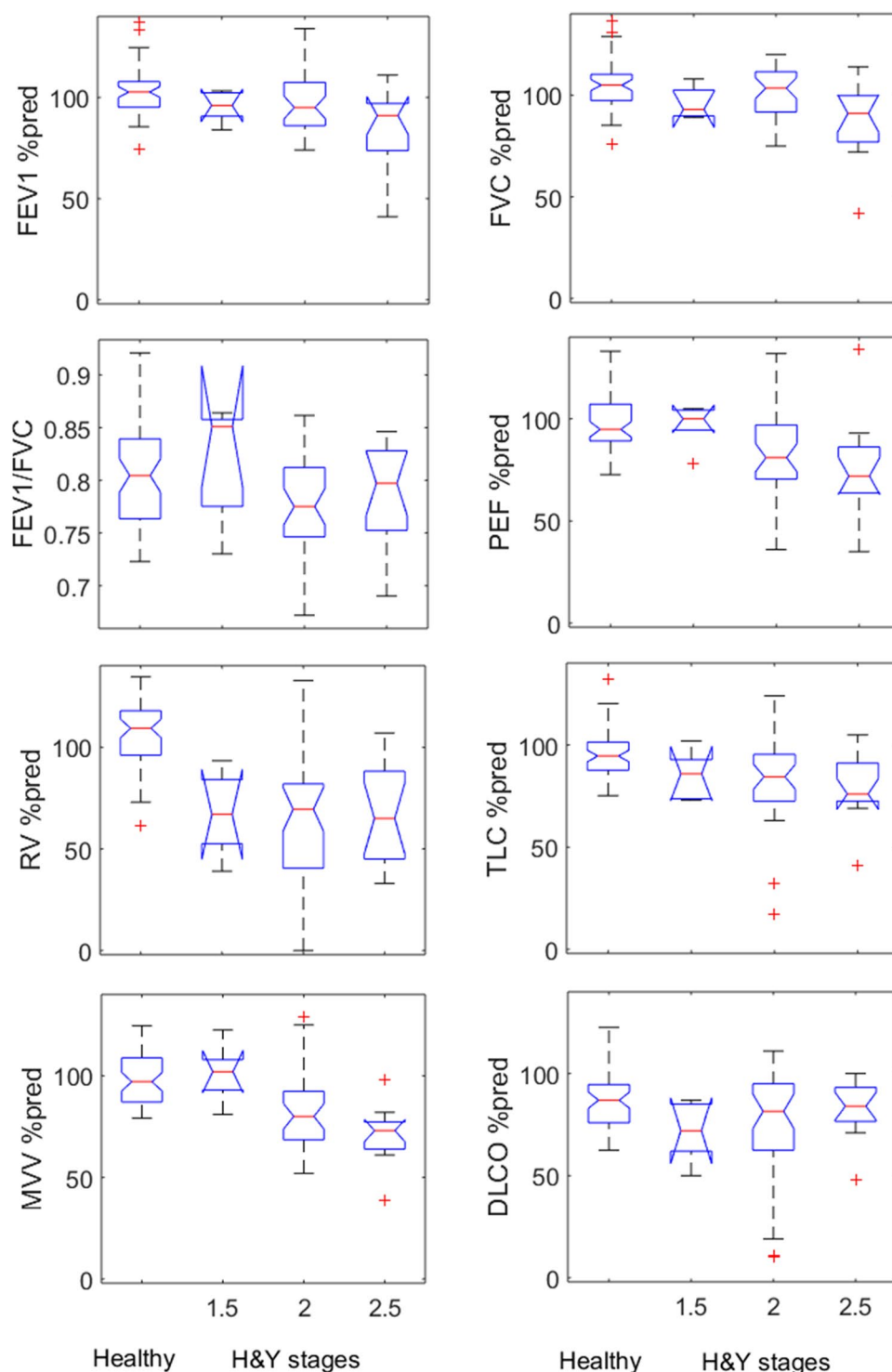
Discussions and Conclusion

In this study, we investigated the pulmonary function of patients with early PD. Similar to some of the previous studies, our patients had both obstructive and restrictive dysfunctions. MVV could be the most sensitive parameter for distinguishing the severity of PD during the early stages.

Respiratory muscle dysfunction is often observed in PD patients [17]. Some studies have suggested that the pathological changes in PD occur first in the medulla [1], which is known to control respiratory depth and rate. However, the restrictive respiratory dysfunction pattern in PD is not yet fully understood. It may be associated with abnormal function of the accessory respiratory muscles, abnormal ventilatory control, and increased chest wall rigidity [18]. Studies have reported upper airway obstruction in PD, which is associated with tremor, bradykinesia, and dystonia [19].

Consequently, the reduction in respiratory muscle strength might lead to a deterioration of pulmonary function. A recent review has showed that respiratory training may improve pulmonary function [20]. Although the parameters PEF and MIP are associated with muscle strength, they might not be sensitive enough to distinguish the reduction in the respiratory muscle strength at various early H&Y stages [7]. Zhang et al. conducted a study that included only patients with H&Y Stage 1 and healthy controls [6]. In their study, MIP %predicted was 38.82±16.87 for PD and 53.17±16.00 for healthy controls. Compared with the MIP %predicted in our study (Fig. 1), their results were extremely low for both PD and healthy controls. Since the details were not given in the Zhang et al. study, we speculated that the training of the subjects and the predicted values used in the studies were different. Nevertheless, MVV reflects the muscle endurance, which appears to be affected in the early stages of PD. Only a few studies investigated MVV in early PD patients. Polatli et al. proposed that MVV was the most affected parameter correlated with the PD severity [21]. In that study, 21 PD patients from H&Y Stages 1 to 3 were included. When testing MVV, the patient is required to exhale and inhale maximally and deeply at the fastest rate, preferably for 12 s. The procedure requires the patient to have some respiratory muscle strength and endurance. As PD is a neuromuscular disease that impairs the strength and endurance of the patient's respiratory muscles, MVV is a more sensitive indicator of thoracic activity and airway resistance. Therefore, our findings further support the use of MVV to help assess

Fig. 1 Comparison of pulmonary function parameters at different H&Y stages. *H&Y stage* Hoehn and Yahr (H&Y) stage; *%pred* percent predicted; *FEV₁* forced expiratory volume during the first second; *FVC* forced vital capacity; *PEF* peak expiratory flow; *RV* residual volume; *TLC* total lung capacity; *MVV* maximal voluntary ventilation; *DLCO* diffusing capacity of the lung for carbon monoxide



patients' neurophysiological conditions due to pulmonary impairment.

One major limitation of this study was the small number of subjects at various PD stages. Moreover, the study was conducted at a single time point without measuring the differences in pulmonary functions during an “off” state. Future studies should include more patients at various PD stages

with motor fluctuations. Another limitation was that we classified PD patients only according to the H&Y stage. The H&Y stages are defined based on mobility, without considering mental, behavioral, or other non-motor problems. This may be irrelevant in patients with mild motor symptoms, but may influence the evaluation of patients with moderate or severe non-motor symptoms. The correlation between

pulmonary function, PD stages, and non-motor symptoms should be investigated in further studies.

Acknowledgments The study was partially supported by Beijing Rehabilitation Hospital of Capital Medical University funding (2020-070).

Author Contributions JX, HJ and ZZ designed the study. CZ, JD YL and GN acquired the data. ML, BZ, JW, YL and BF analyzed and interpreted the data. CZ, JD, YL and ZZ drafted the article. The other authors revised the article critically. All authors approved the final version.

Funding The study was partially supported by Beijing Rehabilitation Hospital of Capital Medical University funding (2020-070).

Declarations

Conflict of interest The authors have no conflict of interest to report.

Ethical Approval This prospective observational study was approved by the Ethics Committee in the Beijing Rehabilitation Hospital, Capital Medical University (No. 2019bkky-001).

Consent to Participate Written informed consent was obtained from all patients prior to the study.

Consent to Publish Not applicable.

References

- Braak H, Del Tredici K, Rub U, de Vos RA, Jansen Steur EN, Braak E (2003) Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol Aging* 24:197–211
- Schrag A, Horsfall L, Walters K, Noyce A, Petersen I (2015) Pre-diagnostic presentations of Parkinson's disease in primary care: a case-control study. *Lancet Neurol* 14:57–64
- Parkinson J (2002) An essay on the shaking palsy. 1817. *J Neuropsychiatry Clin Neurosci* 14:223–236 (**discussion 222**)
- Storch A, Schneider CB, Wolz M, Sturwald Y, Nebe A, Odin P, Mahler A, Fuchs G, Jost WH, Chaudhuri KR, Koch R, Reichmann H, Ebersbach G (2013) Nonmotor fluctuations in Parkinson disease: severity and correlation with motor complications. *Neurology* 80:800–809
- Guilherme EM, Moreira RFC, de Oliveira A, Ferro AM, Di Lorenzo VAP, Gianlorenco ACL (2021) Respiratory disorders in Parkinson's disease. *J Parkinsons Dis* 11:993–1010
- Zhang W, Zhang L, Zhou N, Huang E, Li Q, Wang T, Ma C, Li B, Li C, Du Y, Zhang J, Lei X, Ross A, Sun H, Zhu X (2019) Dysregulation of respiratory center drive (P0.1) and muscle strength in patients with early stage idiopathic Parkinson's disease. *Front Neurol* 10:724
- Santos RBD, Fraga AS, Coriolano M, Tiburtino BF, Lins OG, Esteves ACF, Asano NMJ (2019) Respiratory muscle strength and lung function in the stages of Parkinson's disease. *J Bras Pneumol* 45:e20180148
- Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, Obeso J, Marek K, Litvan I, Lang AE, Halliday G, Goetz CG, Gasser T, Dubois B, Chan P, Bloem BR, Adler CH, Deuschl G (2015) MDS clinical diagnostic criteria for Parkinson's disease. *Mov Disord* 30:1591–1601
- Goetz CG, Poewe W, Rascol O, Sampaio C, Stebbins GT, Counsell C, Giladi N, Holloway RG, Moore CG, Wenning GK, Yahr MD, Seidl L (2004) Movement Disorder Society Task Force report on the Hoehn and Yahr staging scale: status and recommendations. *Mov Disord* 19:1020–1028
- Morris JC (1993) The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology* 43:2412–2414
- Graham BL, Steenbruggen I, Miller MR, Barjaktarevic IZ, Cooper BG, Hall GL, Hallstrand TS, Kaminsky DA, McCarthy K, McCormack MC, Oropez CE, Rosenfeld M, Stanojevic S, Swanney MP, Thompson BR (2019) Standardization of spirometry 2019 update. An official American Thoracic Society and European Respiratory Society technical statement. *Am J Respir Crit Care Med* 200:e70–e88
- Graham BL, Brusasco V, Burgos F, Cooper BG, Jensen R, Kendrick A, MacIntyre NR, Thompson BR, Wanger J (2017) 2017 ERS/ATS standards for single-breath carbon monoxide uptake in the lung. *Eur Respir J*. <https://doi.org/10.1183/13993003.00016-2016>
- Kor AC, Ong KC, Earnest A, Wang YT (2004) Prediction of the maximal voluntary ventilation in healthy adult Chinese subjects. *Respirology* 9:76–80
- Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, Enright PL, Hankinson JL, Ip MS, Zheng J, Stocks J (2012) Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. *Eur Respir J* 40:1324–1343
- Rochester D, Arora N (1983) Respiratory muscle failure. *Med Clin North Am* 67:573–597
- Goetz CG, Fahn S, Martinez-Martin P, Poewe W, Sampaio C, Stebbins GT, Stern MB, Tilley BC, Dodel R, Dubois B et al (2007) Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): process, format, and clinimetric testing plan. *Mov Disord* 22:41–47
- Wrede A, Margraf NG, Goebel HH, Deuschl G, Schulz-Schaeffer WJ (2012) Myofibrillar disorganization characterizes myopathy of camptocormia in Parkinson's disease. *Acta Neuropathol* 123:419–432
- Pal PK, Sathyaprabha TN, Tuhina P, Thennarasu K (2007) Pattern of subclinical pulmonary dysfunctions in Parkinson's disease and the effect of levodopa. *Mov Disord* 3:420–424
- Jankovic J (2008) Parkinson's disease: clinical features and diagnosis. *J Neurol Neurosurg Psychiatry* 79:368–376
- van de Wetering-van Dongen VA, Kalf JG, van der Wees PJ, Bloem BR, Nijkrake MJ (2020) The effects of respiratory training in Parkinson's disease: a systematic review. *J Parkinsons Dis* 10:1315–1333
- Polatli M, Akyol A, Cildag O, Bayulkem K (2001) Pulmonary function tests in Parkinson's disease. *Eur J Neurol* 8:341–345

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.