

Respiratory changes in Parkinson's disease may be unrelated to dopaminergic dysfunction

Alterações respiratórias na doença de Parkinson podem não ter relação com a disfunção dopaminérgica

Luciana Ulhôa Guedes¹, Juliana Melo Rodrigues², Aline Andrioni Fernandes³, Francisco E. Cardoso⁴, Verônica Franco Parreira⁵

ABSTRACT

Objective: To investigate the maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) in patients with Parkinson's disease (PD) during the on and off periods of levodopa and to compare with healthy controls. **Methods:** Twenty-six patients were analyzed with Hoehn and Yahr scores (2–3) and 26 age and gender matched-controls. Statistical analysis was performed with Student's *t*-test for paired and independent samples. **Results:** MIP and MEP values in patients were significantly lower than the values obtained in controls both for off and on stages — excepted for MIP in women ($p=0.28$). For patients with PD, the studied parameters did not differ between stages on and off, with the exception of MEP in women ($p=0.00$). **Conclusions:** Patients with PD have respiratory pressure lower than controls, even in early stages of the disease, and dopamine replacement has little impact over these respiratory pressures. These findings suggest that respiratory changes in PD may be unrelated to dopaminergic dysfunction.

Key words: Parkinson's disease, levodopa, breathing, muscle strength, assessment.

RESUMO

Objetivo: Investigar as pressões inspiratórias máximas (Plmáx) e as pressões expiratórias máximas (PEmáx) em pacientes com doença de Parkinson (DP) durante períodos *on* e *off* e comparar com controles. **Métodos:** Foram estudados 26 pacientes com scores de Hoehn e Yahr (2–3) e 26 indivíduos saudáveis pareados sexo e idade. A análise estatística foi realizada com o teste *t* de Student para amostras pareadas e para amostras independentes. **Resultados:** Os valores de Plmáx e PEmáx nos pacientes foram significativamente menores que os valores observados nos controles, tanto no período *off* como no período *on* — exceto Plmáx nas mulheres ($p=0,28$). Nos pacientes com DP, os parâmetros estudados não diferiram entre os estágios *off* e *on* (exceto PEmáx nas mulheres- $p=0,00$). **Conclusões:** Pacientes com DP têm pressões respiratórias inferiores a controles mesmo em estágios iniciais da doença, e a reposição de dopamina tem pouco impacto sobre pressões respiratórias. Esses achados sugerem que as alterações respiratórias na DP podem não estar relacionadas às disfunções dopaminérgicas.

Palavras-Chave: doença de Parkinson, levodopa, respiração, força muscular, avaliação.

James Parkinson already described the presence of respiratory abnormalities in Parkinson's disease (PD)¹. It has been shown that patients with PD may have an array of respiratory abnormalities and it is well recognized that aspiration pneumonia and pulmonary embolism are the main causes of death in PD^{2,3}. However, it has also been suggested that respiratory symptoms may not be reported or noticed early

because individuals with PD may reduce their levels of activity, lead a very sedentary life, thus never being able to experience any respiratory deficit^{4,6}.

Not many studies describe details concerning respiratory changes in patients with PD. The findings reported in literature include tachypnea, dyspnea and irregularities in the respiratory rhythm, restrictive pulmonary function, dysfunction

¹Rehabilitation Science Graduation Program, School of Physical Education, Physical Therapy and Occupational Therapy; Universidade Federal de Minas Gerais (UFMG), Belo Horizonte MG, Brazil;

²Sarah Kubitschek Hospital, Belo Horizonte MG, Brazil;

³Student, Department of Physical Therapy, School of Physical Education, Physical Therapy and Occupational Therapy; UFMG, Belo Horizonte MG, Brazil;

⁴Full Professor, Movement Disorders Unit; Neurology Service; Department of Internal Medicine; Medical School; UFMG, Belo Horizonte MG, Brazil;

⁵Full Professor, Department of Physical Therapy, School of Physical Education, Physical Therapy and Occupational Therapy; UFMG, Belo Horizonte MG, Brazil.

Correspondence: Verônica Franco Parreira; Laboratório de Avaliação e Pesquisa em Desempenho Cardiorrespiratório, Departamento de Fisioterapia, UFMG; Avenida Antônio Carlos 6.627; 31270-901 Belo Horizonte MG - Brazil; E-mail: veronicaparreira@yahoo.com.br / veronica.parreira@pesquisador.cnpq.br

Conflict of interest: There is no conflict of interest to declare.

Received 09 June 2012; Received in final form 04 July 2012; Accepted 11 July 2012

in upper airways, as well as decreased respiratory pressure^{1,3,4}. Measuring maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) is useful to quantify the degree of respiratory impairment in individuals with PD^{6,7}, and it is also a good method to assess the functional efficiency of respiratory muscles. Observations of respiratory muscle weakness are consistent with the reduced ability to generate normal forced expiratory maneuvers⁸. Muscle weakness in patients with PD restricts the ability to overcome rigidity and potentially contributes to reduced lung volume and respiratory pressure, which will impact on swallow, cough and speech functions⁷.

Black and Hyatt⁹ developed a noninvasive, fast and reliable method to measure MIP and MEP. These variables reflect the static pressure generated in the mouth during maximal inspiratory and expiratory efforts¹⁰. The changes of these parameters have been well characterized in a myriad of neuromuscular disorders¹¹.

Several investigators have studied MIP and MEP in PD. In some of these studies, authors have failed to find differences between these parameters in comparison with controls and/or predicted values. For instance, MIP values of nine patients with PD according to Hoehn and Yahr (HY) scores ranged from 1 to 3, and they did not differ from values of control subjects in one study⁸. In another study with 16 patients (HY 1 to 3), MIP and MEP were within the range predicted for their age and gender¹². Similarly, 40 patients with PD (HY 1 to 3) had MIP and MEP comparable to those found in controls¹³.

Silverman et al.⁷ evaluated MIP and MEP of 28 patients with PD (mean age of 64 years and HY 2 to 3), comparing them with reference values established by Enright et al.¹⁴. They found that in the group of patients with PD 69.2% of MIP values were within or above normal ranges. On the other hand, only 28.6% showed MEP within normal ranges. No participants had MEP values above normal. The authors concluded that MIP was less affected at baseline than MEP, since most participants were within normal ranges.

On the other hand, other studies have found differences between patients with PD and controls. Vincken et al.¹, for instance, determined respiratory pressure of patients with PD as HY 1 to 5. Regardless of the presence of upper airway evidence, they found an average reduction of 61% of both MIP and MEP in comparison to values predicted for matched-controls. Similar findings were reported by Sabaté et al.⁵, who studied 58 patients with PD (HY 1 to 5, mean age of 68 years, and average duration of illness of 5.8 years). MIP and MEP values in PD were 25 ± 17 H₂Ocm and 38 ± 13 H₂Ocm, respectively, whereas in controls these pressures were 52 ± 24 H₂Ocm and 63 ± 23 H₂Ocm. The differences were statistically significant. These results were reproduced by another investigation with 23 patients with PD, which found significant reduction of MEP both in comparison to controls and predicted values. Weiner et al.¹⁵ studied 20 patients with PD, HY 2 to 3, mean age of 66 years and compared them to 20 healthy age and

gender matched-controls. MIP and MEP values were significantly lower in patients with PD. Similarly, the maximum respiratory pressure of 66 patients with PD (HY 1 to 4, mean age of 63 years and average duration of illness of 6 years) was significantly lower than the values obtained in the age matched control group as well as when compared to predicted values⁶.

The mechanism responsible for respiratory pressure changes is yet to be determined and is described in at least part of the patients with PD. Some suggest that these findings are a result of deformities in the spine and chest walls, commonly seen in PD⁵. There is also evidence that support the role of central nervous system dysfunction in the pathogenesis of these findings. In one investigation performed with 10 patients (HY 2 to 4), the authors described a statistically significant increase of MIP and MEP after administration of apomorphine. These results suggest that nigrostriatal dysfunction is at least partly responsible for the decrease of respiratory pressure in patients with PD⁴. There are few publications in literature concerning the effect of levodopa on MIP and MEP^{15,16}.

The aim of this study was to determine MIP and MEP in patients with PD, comparing these values with those found in matched-controls and to evaluate the effect of levodopa administration over these variables.

METHODS

Participants

We enrolled 26 patients who met the UK Brain Bank Criteria for PD¹⁷, HY score 2 to 3, aged between 50 and 75 years, stable antiparkinsonian regimen for at least 30 days. They must not have undergone surgery for PD, with minimal status examination superior to 24, body mass index lower than 30 kg/m², absence of cardio-respiratory disorders; they also could not be smokers. We also studied 26 age and gender matched healthy controls. The study was approved by the Ethics Committee of our Institution.

Measurements

Maximum respiratory pressure was measured by a manovacuometer with operational break of -300 to +300 H₂Ocm (GeRar[®] São Paulo, Brazil), using the protocol described by Neder et al.¹⁸. There were two initial training sessions followed by five sessions with a one-minute interval between them. With this procedure, respiratory pressure ranged less than 10% in at least three of the sessions. The highest values of MIP and MEP were used for statistical analysis. Patients with PD had their pressure measured during the practically defined *off* state (12 hours of antiparkinsonian drug withdrawal), and during the *on* state (60 minutes after the intake of medications). Prior to the first measurement, a complete Unified Parkinson's Disease Rating Scale (UPDRS)¹⁹ was applied, whereas just part III was obtained during the *on* state.

Control subjects had respiratory pressure measurements performed once, according to the same guidelines. Regression equations proposed by Neder et al.¹⁸ to calculate the predicted values of the maximum respiratory pressure in relation to age and gender for the Brazilian population were used.

Statistical analysis

Statistical analysis was performed with SPSS (Version 10.0, Illinois, USA). Shapiro-Wilk test was used to check the normal distribution of variables whereas Student's *t*-test was employed for paired samples in order to compare states *on* and *off* in patients with PD and control group. Because of the gender's influence on respiratory pressure, we studied females and males separately. Significance level was established at 5%.

RESULTS

Table 1 presents the demographic features of the subjects enrolled in the study: 26 patients with PD and 26 age and gender matched-controls.

Table 2 shows UPDRS scores of *off* and *on* states. It was observed that scores were significantly higher during the *off* state in comparison to the *on* state, for both females and males.

Table 3 shows MIP and MEP values for patients and controls. Both women and men with PD presented with lower values during the *off* state in relation to controls. Concerning the *on* stage, there are no significant differences of MIP between females with PD and controls. Comparison of *on* and *off* state variables between patients with PD confirmed the little impact of the antiparkinsonian treatment on respiratory pressure because only the MEP of women significantly increased after using the medications.

Table 4 demonstrates that overall the respiratory pressures of both patients and controls are below those expected for the Brazilian population. The exceptions are MEP values of male and female controls.

DISCUSSION

Our findings confirm the observation of others authors, according to which respiratory pressure in PD is lower than that found in healthy age and gender matched-controls, as well as in relation to values predicted for the population^{1,3,5,6}. Since we have studied subjects with HY 2 to 3, our results indicate that respiratory dysfunction is already present in early stages of PD. We have also replicated the literature finding showing that gender influences respiratory pressures^{9,20}. Harik-Khan et al.²⁰, for instance, demonstrated that MIP values in healthy men are 30% higher than those found in age-matched women.

Table 1. Demographic and clinical features of studied subjects.

	Controls	Patients	p-value
Male/Female	16/10	16/10	–
Age (years)	64±7	63±7	0.76
PD duration (years)		9.1±0.3	–
Daily levodopa doses (mg)		364±316	–

Data presented as mean±standard deviation; PD: Parkinson's disease.

Table 2. Unified Parkinson's disease rating scale scores of patients.

	<i>off</i>	<i>on</i>	p-value
Total females	51.2 ± 19.3	42.7 ± 17.3	0.001
Total males	60.3 ± 14.1	44.4 ± 12.8	0.001
Part III females	26.5 ± 13.1	18.0 ± 11.6	0.001
Part III males	34.3 ± 8.3	18.3 ± 6.4	0.001

Data presented as mean±standard deviation; *off* refers to "without levodopa" and *on* refers to "with levodopa".

It is interesting that some investigations about respiratory pressure present in literature failed to find differences between patients with PD and values predicted for the general population or controls^{8,12,13}. The discrepancy in results of different studies most likely reflects methodological issues: 1) Some of the studies^{7,12} compared the values of variables with those predicted for the population, not including controls. As we have shown (Table 4), there is a difference between the values predicted for the Brazilian population and the controls included in our study; 2) Other investigations used non-matched controls; 3) Because of the influence of the gender over the respiratory pressure, demonstrated by our study and others^{7,9,15,20}, it is mandatory not only to use age, but also gender matched-controls, which did not happen in many of the studies on PD⁶; 4) In some of the studies, it is not clear whether or not the pressures were measured when the patients were on the effect of the antiparkinsonian medications; 5) Diagnostic criteria of PD have not been described in some of the investigations. This raises the issue of the possibility to include patients with parkinsonian disorders other than PD; 6) Finally, there has been a wide severity variation concerning the parkinsonian syndrome among the patients included in some of these studies, with HY score ranging from 1 to 5.

Few studies investigate the effect of levodopa on respiratory pressure. One report, however, described that subcutaneous injections of apomorphine, a powerful direct dopamine receptor agonist, induced a statistically significant increase of MIP and MEP in 10 patients with PD (HY 2 to 4)⁴. There is also a single case report which described the reversibility of upper airway obstruction in a patient with PD after using levodopa¹⁶. On the contrary, Weiner et al.¹⁵ observed MIP and MEP comparing *off* and *on* periods in 20 patients with PD. These variables tended to increase during *on* periods, however, it did not reach statistical significance. In this study, we have found that levodopa caused MIP

Table 3. Values of maximal inspiratory pressure and maximal expiratory pressure in Parkinson's disease patients and controls.

	Controls	Patients-Off	Patients-on	p-value
MIP women	70.0±14.1	50.0±22.9	55.6±18.8	0.04* 0.28 0.33
MEP women	105.6 ±19.4	55.6±18.8	64.4±21.9	0.00* 0.00** 0.00***
MIP men	86.9 ± 6.2	61.9±17.2	65.0±17.9	0.00* 0.00** 0.42
MEP men	120.0 ±29.4	74.4±15.9	81.9±14.7	0.00* 0.00** 0.07

Data presented as mean±standard deviation (cmH₂O); *off* refers to "without levodopa"; *on* refers to "with levodopa"; *p-value for patients-*off* versus controls; **p-value for patients-*on* versus controls; ***p-value for patients-*off* versus patients-*on*. MIP: maximal inspiratory pressure; MEP: maximal expiratory pressure.

Table 4. Percentage of maximal inspiratory pressure and maximal expiratory pressure in Parkinson's disease patients and controls.

	Controls (%)	off (%)	on (%)
MIP women	94.7	66.7	62.3
MEP women	133.6	71.7	80.6
MIP men	80.2	62.3	62.1
MEP men	133.6	71.7	80.6

% refers to values predicted for the Brazilian population; *off* refers to "without levodopa"; *on* refers to "with levodopa". MIP: maximal inspiratory pressure; MEP: maximal expiratory pressure.

values in women to significantly increase. One may speculate that this lack of difference between *on* and *off* states reflects insufficient dopaminergic stimulation. However, the statistically significant differences between *on* and *off* UPDRS scores indicate that the dose of levodopa and other antiparkinsonian drugs was capable of inducing a clinically relevant change in the functional status of the nigrostriatal system. This finding in our study raises the issue that respiratory dysfunction in patients with PD may be unrelated to dopaminergic dysfunction. Such situation would be similar to the occurrence of dysphagia, gait disorder including freezing (motor block) and other features of PD, which are little or not changed by dopamine replacement therapy. In one study, the authors showed that despite unequivocal improvement of motor findings with levodopa, swallowing function presented little improvement²¹.

Similarly, step length and freezing of gait are only partly improved by levodopa replacement²². It is worth mentioning that in contrast to dysphagia and gait disorder, which occur after long duration of PD, our findings suggest that respiratory pressure changes are an early symptom of PD. Finally, data from other studies suggest that MIP and MEP changes may worsen with the progression of the illness^{6,14}.

The pathogenesis of respiratory pressure changes in PD is yet to be determined. Some authors have shown respiratory function improvement in PD with dopamine treatment^{1,4}, whereas others did not find any respiratory improvement with the action of levodopa^{15,23}. However, these findings were not explained by the improvement in pulmonary function or respiratory muscle. The authors suggested that it was possibly caused due to a central effect. The presence of dopamine receptors in central and peripheral structures²⁴ may suggest that dopamine dysfunction leading to a direct negative effect on the respiratory structures, as well as to rigidity and bradykinesia of the respiratory muscles, is the causative mechanism of MIP and MEP abnormalities⁴. This hypothesis is weakened, however, by the dissociation between the action of levodopa on UPDRS scores and the respiratory values found in our study. The suggestion that deformities in the thoracic cage lead to respiratory abnormalities⁵ also seems unlikely, since none of our patients presented with such findings. Considering the little improvement of respiratory changes in PD after the use of levodopa, one may speculate that dopaminergic and non-dopaminergic central changes play a role in the pathogenesis of these abnormalities.

Finally, none of our patients presented respiratory complaints (data not shown) despite the low values of respiratory pressure. In fact, just moderate to severe reductions in respiratory pressure, 40% below normal values, are regarded as a respiratory disorder²⁵. Nevertheless, the decrease of these variables is a risk factor for pulmonary dysfunction, since it increases the risk of atelectasis and others²⁴.

Finally, our results demonstrated that the pressure of patients with Parkinson's disease is lower than of that in control subjects, even in early stages of the disease. Dopamine replacement has little impact on these respiratory variables, suggesting that early intervention to improve respiratory function in PD may be necessary.

References

1. Vincken WG, Gauthier SG, Dollfuss RE, Hanson RE, Darauay CM, Cosio MG. Involvement of upper-airway muscles in extrapyramidal disorders. A cause of airflow limitation. *N Engl J Med* 1984;311:438-442.
2. Hovestadt A, Bogaard JM, Meerwaldt JD, van der Meché FG, Stigt J. Pulmonary function in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1989;52:329-333.
3. Fontana GA, Pantaleo T, Lavorini F, Benvenuti F, Gangemi S. Defective motor control of coughing in Parkinson's disease. *Am J Respir Crit Care Med* 1998;158:458-464.
4. de Bruin PF, de Bruin VM, Lees AJ, Pride NB. Effects of treatment on airway dynamics and respiratory muscle strength in Parkinson's disease. *Am Rev Respir Dis* 1993;148:1576-1580.
5. Sabaté M, Rodríguez M, Méndez E, Enríquez E, González I. Obstructive and restrictive pulmonary dysfunction increases disability in Parkinson disease. *Arch Phys Med Rehabil* 1996;77:29-34.
6. Haas BM, Trew M, Castle PC. Effects of respiratory muscle weakness on daily living function, quality of life, activity levels, and exercise capacity in mild to moderate Parkinson's disease. *Am J Phys Med Rehabil* 2004;83:601-607.
7. Silverman EP, Sapienza CM, Saleem A, et al. Tutorial on maximum inspiratory and expiratory mouth pressures in individuals with idiopathic Parkinson disease (IPD) and the preliminary results of an expiratory muscle strength training program. *NeuroRehabilitation* 2006;21:71-79.
8. Tzelepis GE, McCool FD, Friedman JH, Hoppin FG Jr. Respiratory muscle dysfunction in Parkinson's disease. *Am Rev Respir Dis* 1988;138:266-271.
9. Black LF, Hyatt RE. Maximal respiratory pressures: normal values and relationship to age and sex. *Am Rev Respir Dis* 1969;99:696-702.
10. McConnell AK, Copestake AJ. Maximum static respiratory pressures in healthy elderly men and women: issues of reproducibility and interpretation. *Respiration* 1999;66:251-258.
11. Berry JK, Vitalo CA, Larson JL, Patel M, Kim MJ. Respiratory muscle strength in older adults. *Nurs Res* 1996;45:154-159.
12. Canning CG, Alison JA, Allen NE, Groeller H. Parkinson's disease: an investigation of exercise capacity, respiratory function, and gait. *Arch Phys Med Rehabil* 1997;78:199-207.
13. Cardoso SR, Pereira JS. [Analysis of breathing function in Parkinson's disease]. *Arq Neuropsiquiatr* 2002;60:91-95.
14. Enright PL, Kronmal RA, Manolio TA, Schenker MB, Hyatt RE. Respiratory muscle strength in the elderly. Correlates and reference values. Cardiovascular Health Study Research Group. *Am J Respir Crit Care Med* 1994;149:430-438.
15. Weiner P, Inzelberg R, Davidovich A, et al. Respiratory muscle performance and the Perception of dyspnea in Parkinson's disease. *Can J Neurol Sci* 2002;29:68-72.
16. Vincken WG, Darauay CM, Cosio MG. Reversibility of upper airway obstruction after levodopa therapy in Parkinson's disease. *Chest* 1989;96:210-212.
17. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry* 1992;55:181-184.
18. Neder JA, Andreoni S, Lerario MC, Nery LE. Reference values for lung function tests. II. Maximal respiratory pressures and voluntary ventilation. *Braz J Med Biol Res* 1999;32:719-727.
19. Fahn S, Elton R, and members of the UPDRS Development Committee. Unified Parkinson's Disease Rating Scale. In: Fahn S, Marsden C, Calne D, Goldstein M (eds). *Recent development in Parkinson's disease*. Florham Park, NJ: Macmillan Health Care Information; 1987: 153-164.
20. Harik-Khan RI, Wise RA, Fozard JL. Determinants of maximal inspiratory pressure. The Baltimore Longitudinal Study of Aging. *Am J Respir Crit Care Med* 1998;158:1459-1464.
21. Hunter PC, Cramer J, Austin S, Woodward MC, Hughes AJ. Response of parkinsonian swallowing dysfunction to dopaminergic stimulation. *J Neurol Neurosurg Psychiatry* 1997; 63:579-583.
22. Morris M, Iansek R, McGinley J, Matyas T, Huxham F. Three-dimensional gait biomechanics in Parkinson's disease: evidence for a centrally mediated amplitude regulation disorder. *Mov Disord* 2005;20:40-50.
23. Obenour WH, Stevens PM, Cohen AA, McCutchen JJ. The causes of abnormal pulmonary function in Parkinson's disease. *Am Rev Respir Dis* 1972;105:382-387.
24. Rice JE, Antic R, Thompson PD. Disordered respiration as a levodopa-induced dyskinesia in Parkinson's disease. *Mov Disord* 2002;17: 524-527.
25. Hautmann H, Hefele S, Schotten K, Huber RM. Maximal inspiratory mouth pressures (PIMAX) in healthy subjects--what is the lower limit of normal? *Respir Med* 2000;94:689-693.