

Assessment of the acute effects of different PEP levels on respiratory pattern and operational volumes in patients with Parkinson's disease[☆]

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1. Introduction

Parkinson's is a chronic progressive neurodegenerative disorder characterized by a profound and selective loss of nigrostriatal dopaminergic neurons with the presence of eosinophilic, intracytoplasmic, proteinaceous inclusions (Lewy bodies) and dystrophic Lewy neuritis in the remaining neurons (Shobha et al., 2006; Thomas and Beal, 2007).

Parkinson's clinical alterations such as loss of movement control may influence the respiratory system (Sande de Souza et al., 2011; Brown et al., 1997). It has been reported that the reduction of thoracic motion (Cardoso and Pereira, 2002; Pal et al., 2007), which results from posture alterations and osteoarticular degeneration, leads to an alteration in the spinal axis that affects breathing mechanics (Köseoğlu et al., 1997). Phasic and tonic activity alterations of respiratory muscles may also affect the respiratory system. Several studies have observed restrictive breathing pattern characteristics in patients suffering from

Parkinson's with diminished lung function and reduced respiratory muscles endurance and strength (De Pandis et al., 2002; Polatli et al., 2001), as well as a decreased pulmonary compliance (Sabaté et al., 1996; Brown, 1994).

Different types of respiratory therapies have been developed recently, with the aim of decreasing or minimizing possible complications caused by lung restriction. The application of Positive expiratory Pressure (PEP) represents a reliable, safe and low-cost intervention that allows increasing lung volumes and intrathoracic pressure (Ricksten et al., 1986; Myers, 2007). Although positive pressure therapy has been used in other respiratory and cardiac diseases (Mortensen et al., 1991; Placidi et al., 2006), the possible physiologic effects that different intensities of PEP may cause in chest volumes in Parkinson's patients remains unknown.

PEP has been used to improve lung volume and consequently oxygenation. More specifically, PEP improves collateral ventilation, airways clearance, O₂ distribution and increases functional residual capacity. PEP also avoids small airways collapse, promotes greater ventilation and increases expiratory time (Mestriner et al., 2009; Fink, 2002).

The aim of the present study was to determine the acute effects of different levels of PEP on breathing pattern, operational volumes of the chest wall and its different compartments (pulmonary rib cage, abdominal rib cage and abdomen) and shortening velocity of respiratory muscles on patients with Parkinson's.

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2. Methods

2.1. Subjects

Subjects diagnosed with Parkinson's disease and a control group of healthy individuals, matched for age, gender and body mass index, were recruited for the study. Parkinson's subjects inclusion criteria were patients diagnosed with stages II or III of Parkinson's disease according to the Hoehn and Yahr scale (Hoehn and Yahr, 1967), subjects during "ON" condition, which is, under the effects of Levodopa and not exhibiting cognitive disorders that could affect patients' collaboration during the experimental procedures. Individuals showing pulmonary alterations, others than the ones caused by Parkinson's and mask discomfort as well as cognitive disorders were excluded from the study. The study was approved by the Onofre Lopes University Hospital Research Ethics Committee (protocol no. 063/2011) and all patients signed informed written consent.

2.2. Study design

The subjects from both groups were assessed on a single day, beginning with anamnesis, physical examination consisting of measuring vital signs [(blood pressure (BP), heart rate (HR) and peripheral oxygen saturation (SatO₂)], anthropometric characteristics, spirometry and respiratory muscles strength. Successively, lung volumes were measured before, during and after the experimental protocol using Optoelectronic Plethysmography (OEP, see below).

2.3. Spirometric assessment

The technical procedure, criteria of accessibility, reproducibility, reference and interpretive values, standardization and equipment followed the Brazilian Pneumology Society Guidelines (SBPT, 2002). We used a DATOSPIR 120 (SibelMed Barcelona, Spain) daily calibrated, coupled to a microcomputer. Forced expiratory volume in the first second (FEV₁), forced vital capacity (FVC), forced expiratory flow between 25 and 75% (FEF_{25-75%}), peak expiratory flow (PEF) and the Tiffeneau index (FEV₁/FVC) were considered. The highest spirometric values were considered for analysis and compared with reference values validated for the Brazilian population (Pereira et al., 2007).

2.4. Respiratory muscle strength

Respiratory muscle strength was assessed using a MICRO RPM respiratory pressure meter (Micro Medical Ltd., Kent, England). The tests were conducted with individuals in the sitting position immediately after the pulmonary function test, with a resting period between tests. Before each test, the subjects were thoroughly instructed regarding procedures, and the results obtained were assessed in their absolute and relative values. For each assessment, the maximum value obtained in at most five tests was considered, provided that this value was not greater than 5% between the three tests. The values obtained were compared to a previously described normality curve (SBPT, 2002). The sniff nasal inspiratory pressure (SNIP) test was applied for 10 measures separated by a 30-second resting period and performed from Functional Residual Capacity (FRC) (Heritier et al., 1994), using previously described equations (Araújo et al., 2012) to obtain reference values.

2.5. Optoelectronic plethysmography (OEP)

Volume variations of total chest wall and its compartments, namely pulmonary rib cage (RCp), abdominal rib cage (RCa) and

abdomen (AB) were measured by Optoelectronic plethysmography (Aliverti et al., 2003). The motion of 89 reflective markers positioned on the thoraco-abdominal surface [42 on the anterior thoraco-abdominal wall, 37 on the back and 10 on the two lateral sides (Gorini et al., 1999)] was measured in three dimensions by a set of TV cameras. Volumes were obtained by Gauss Theorem as previously described (Cala et al., 1996; Aliverti and Pedotti, 2003).

2.6. Assessment of chest wall volumes using PEP

PEP was applied by a PEP valve with adjustable load between 0 and 20 cmH₂O (Vital Signs Inc., Totowa, NJ, United States), attached to a face mask (Vital Signs, Atlanta, USA) adapted to fit subjects using headgear. Three different levels of PEP (10, 15 and 20 cmH₂O) were applied in random order to the subjects during chest wall volumes measurement for 5 min. Resting quiet breathing (baseline) values were recorded at the beginning of the protocol. For each PEP level, chest wall volumes were measured during: (a) PEP application and (b) recovery after PEP application. Recovery values, recorded after the use of different levels of PEP, are shown as mean value calculated among the three different moments (after PEP₁₀, PEP₁₅ and PEP₂₀) as they show no differences among them. During data acquisition, the subjects were in the sitting position with hands on thighs and arms away from the trunk.

2.7. Analysis of lung volume variables

From OEP data, the following variables were considered for further analysis: tidal volume of the chest wall (ΔV_{cw}) and its different compartments (ΔV_{rcp} , ΔV_{rca} , ΔV_{ab}); end-expiratory and end-inspiratory total and compartmental chest wall volumes, inspiratory (T_i) and expiratory (T_e) time, total respiratory cycle time (T_{tot}), respiratory rate (RR), total minute ventilation ($\text{MinVent} = \Delta V_{cw} \cdot \text{RR}$), mean inspiratory flow ($\Delta V_{cw}/T_i$) and mean expiratory flow (V_t/T_e). $\Delta V_{ab}/T_i$, $\Delta V_{ab}/T_e$ and $\Delta V_{rcp}/T_i$ were calculated as indexes of diaphragm, expiratory abdominal and inspiratory rib cage muscle shortening velocities as previously described (Aliverti et al., 2002, 2003).

Analyses were carried out disregarding the first and last 30 s of each condition (baseline, PEP, recovery), considering mean data of the 30 most homogeneous seconds of the 240 remaining period.

2.8. Statistical analysis

Statistical procedures were performed using *GraphPadPrism 5.0* software. Sample size was calculated based on standard deviation of ΔV_{cw} in a pilot study with 5 patients. A difference of 0.1 L, with a power of 85% and $p \leq 0.05$ indicated a sample size of 15 patients. The results are presented as mean and standard deviation for parametric variables. Variable normality was assessed with the Shapiro-Wilk test. Unpaired *t*-test was applied for intergroup assessments, and two-way ANOVA with Bonferroni's post hoc to analyze the possible differences between variables studied during the application of different PEP levels in both groups.

3. Results

3.1. Clinical aspects

The Parkinson's group exhibited significantly lower spirometric and respiratory muscle strength values than the control group ($p < 0.01$) (Table 1).

Table 1
Anthropometric, pulmonary function and respiratory muscle strength characteristics of both groups.

	Parkinson's group (n = 15)	Control group (n = 15)	p value
Age (years)	59.07 ± 9.34	58.80 ± 9.02	0.93
BMI (kg/m ²)	25.54 ± 3.03	26.20 ± 2.26	0.50
Gender (M/F)	12/03	12/03	1.0
Diagnosis (years)	4.07 ± 2.84	–	–
FVC (L)	3.09 ± 0.81	3.99 ± 0.93	<0.01
FVC (% pred)	80.8 ± 16.71	96.87 ± 13.46	<0.01
FEV ₁ (L)	2.58 ± 0.65	3.17 ± 0.73	0.02
FEV ₁ (% pred)	85 ± 16.51	96.53 ± 12.12	0.03
FEV ₁ /CVF	0.84 ± 0.06	0.80 ± 0.07	0.13
FEF _{25-75%}	3.23 ± 0.89	3.62 ± 1.18	0.31
FEF _{25-75%} (% pred)	112.1 ± 36.42	119.5 ± 32.69	0.56
PEF (L/s)	5.09 ± 1.39	8.04 ± 1.66	<0.01
PEF (% pred)	54.4 ± 15.82	83 ± 18.62	<0.01
MIP (cmH ₂ O)	82.13 ± 28.59	126.5 ± 46.66	<0.01
MIP (% pred)	78.93 ± 23.33	120.8 ± 34.14	<0.01
MEP (cmH ₂ O)	101.5 ± 21.76	136.7 ± 33.33	<0.01
MEP (% pred)	92.87 ± 17.65	124.7 ± 25.96	<0.01
SNIP (cmH ₂ O)	72.80 ± 23.36	100.7 ± 27.87	<0.01
SNIP (% pred)	70.13 ± 23.09	96.67 ± 25.82	<0.01

BMI: body mass index; FVC: forced vital capacity; FEV₁: forced expiratory volume in the 1st second; FEV₁/FVC: tiffeneau index; FEF_{25-75%}: forced expiratory flow between 25 and 75%; PEF: peak expiratory flow; IP max: maximum inspiratory pressure; EP max: maximum expiratory pressure; SNIP: sniff nasal inspiratory pressure % pred: percentage of predicted.

3.2. Characterization of quiet breathing

We found similar minute ventilation between the groups, however tidal volume was significantly lower ($p < 0.01$) while respiratory rate was slightly higher in Parkinson's compared to controls during quite breathing (Fig. 1). The lower tidal volume was due mostly to a reduced tidal volume of the pulmonary rib cage.

3.3. Effects of PEP on breathing pattern

ΔV_{cw} was lower in Parkinson's group during quiet breathing and at all levels of PEP compared to controls ($p < 0.001$). When we compared QB to PEP levels we found a significant increase in ΔV_{cw} ($p < 0.001$) at all PEP levels in both groups. Parkinson's subjects did not show significant differences between the three PEP levels while control group showed significant differences between PEP₁₀ and PEP₁₅ ($p < 0.05$) and between PEP₁₀ and PEP₂₀ ($p < 0.001$). ΔV for

chest wall compartments was also significantly lower when we compared Parkinson's to controls during all PEP levels ($p < 0.05$). Intragroup analysis also showed significant increase of ΔV for all compartments when we compared QB to PEP levels for both groups ($p < 0.05$) with exception of Rca compartment for Parkinson's that showed significant difference between QB and PEP 20 only (Fig. 2). At recovery period, ΔV_{cw} returned to quiet breathing values in both groups (Fig. 2). We found significant difference in the compartmental distribution of ΔV_{cw} percentage during quiet breathing and at all levels of PEP ($p < 0.0001$) (Fig. 3).

In relation to breathing pattern time variables, Ttot, T_i and T_e were lower in the Parkinson's group when compared to the control group during quiet breathing ($p < 0.0001$). Ttot and T_i were lower in the Parkinson's group ($p < 0.0001$) at all PEP levels. T_e was higher in the Parkinson's group than in the control group only with PEP₁₀ ($p < 0.0001$). Ttot and T_e increased in the Parkinson's group with PEP₁₀ and PEP₂₀ ($p < 0.05$). In relation to T_i, significant differences were observed only during PEP₂₀ ($p < 0.01$). In the control group Ttot increased at all PEP levels ($p < 0.001$), with differences observed between PEP₁₀ and PEP₂₀ ($p < 0.01$), while T_i was higher at all PEP levels ($p < 0.001$). T_e changed only during PEP₁₅ and PEP₂₀ ($p < 0.001$). In the recovery period Ttot, T_i and T_e returned to quiet breathing values.

When we compared QB with different levels of PEP we found that RR is significantly higher at QB in both groups ($p < 0.005$). Intragroup analysis also showed that minute ventilation and mean inspiratory flow are significantly higher during different PEP levels compared to QB for both groups ($p < 0.0001$). Considering an intergroup analysis we found that control group showed higher values for minute ventilation and mean inspiratory flow during all PEP lev-els ($p < 0.001$) while mean expiratory flow was significantly higher at PEP₁₀ only ($p < 0.05$) (Fig. 4).

3.4. Effects of PEP on operational volumes

We found an intergroup difference in end-expiratory chest wall volume (EEV_{cw}) variations at all PEP levels ($p < 0.0001$). EEV_{cw} did not increase in Parkinson's group during different levels of PEP ($p > 0.05$). The control group showed a decrease in EEV_{cw} during PEP₁₅ and PEP₂₀ ($p < 0.05$) with no differences between the levels. A significant difference was observed in end-inspiratory chest wall volume (EIV_{cw}) variation when we compared quiet breathing to all PEP levels in both groups ($p < 0.01$). EIV_{cw} increased in Parkinson's group at all PEP levels without differences between levels ($p < 0.001$). In the control group EIV_{cw} also increased for all PEP levels ($p < 0.001$), and there was a significant difference between PEP₁₀ and PEP₂₀ ($p < 0.01$). When we assessed operational values according to chest wall compartment we found that EEV for Rcp, Rca and Ab were significant different between the groups ($p < 0.05$). EIV values for Rcp were significant different between the groups ($p < 0.005$). We also found that EIV values were significantly higher for Rca and Ab compartments when we compared QB to different levels of PEP ($p < 0.0001$). Operational volumes returned to quiet breathing values during the recovery in both groups (Fig. 5).

3.5. Effects of PEP on respiratory muscles shortening velocity

There was an intergroup difference in the index of shortening velocity of abdominal, diaphragm and inspiratory muscles of the rib cage when we compared QB to PEP Levels ($p < 0.01$). $\Delta V_{ab}/T_e$, used as an index of expiratory abdominal muscles shortening velocity, was not influenced by PEP in Parkinson's group ($p > 0.05$), though the control group exhibited an increase at all PEP levels ($p < 0.01$), without differences between them. $\Delta V_{ab}/T_i$, used as an index of diaphragm shortening velocity, was not influenced by PEP in Parkinson's group ($p > 0.05$), while control group

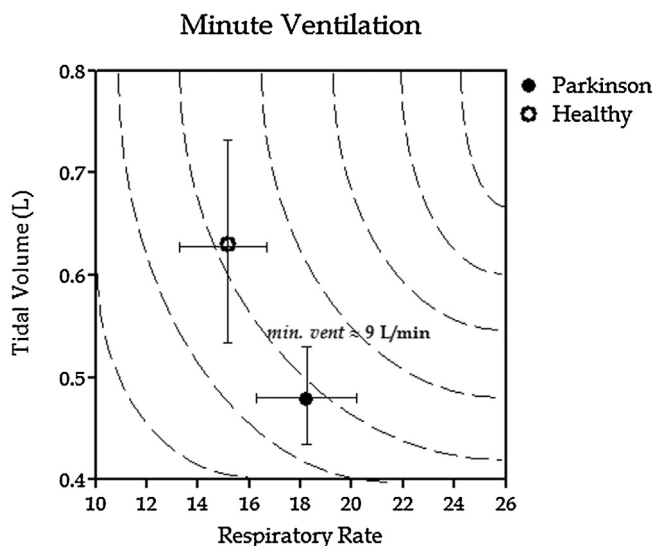


Fig. 1. Minute ventilation in Parkinson's subjects and control group during quite breathing.

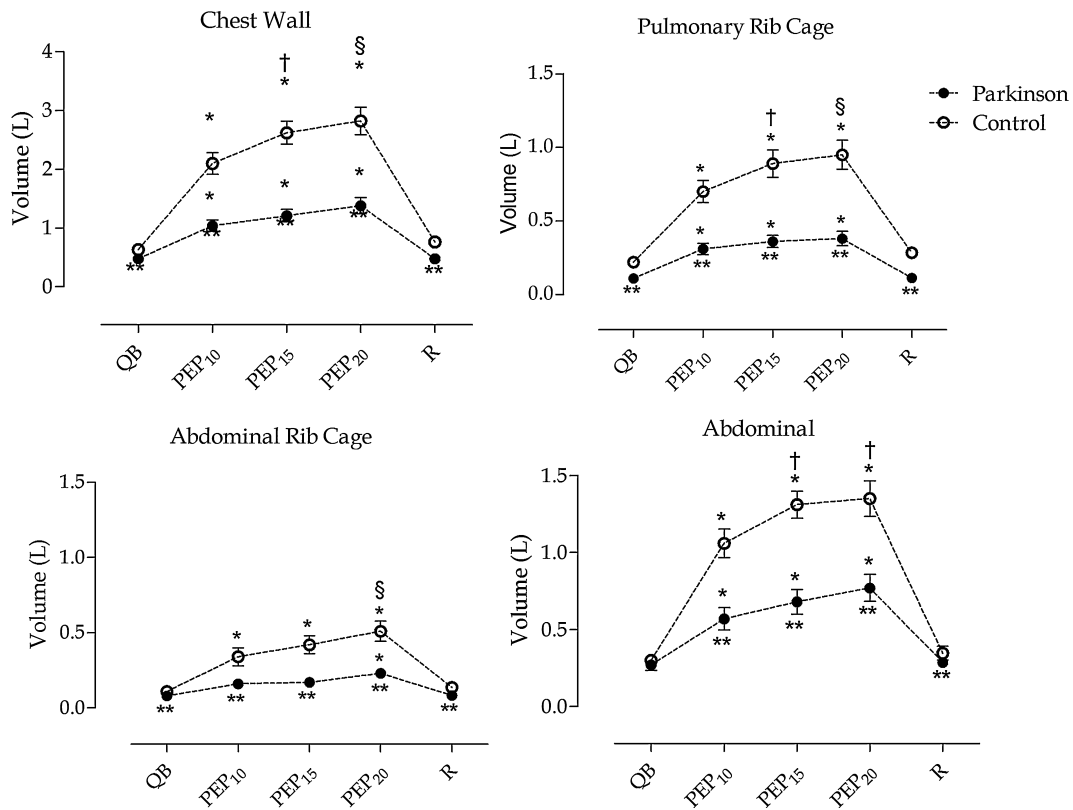


Fig. 2. Effects of PEP on tidal volume of the chest wall and its compartments. QB: quiet breathing. R: recovery. *Intragroup difference comparing quiet breathing, $p < 0.05$. †Intragroup difference comparing PEP₁₀, $p < 0.05$. §Intragroup difference comparing PEP₁₀, $p < 0.01$. **Intergroup differences, $p < 0.05$.

showed an increase at all PEP levels ($p < 0.01$), with no differences between levels. $\Delta V_{\text{rcp}}/T_i$, used as an index of inspiratory rib cage muscles shortening velocity, also increased with PEP in control group ($p < 0.001$), with no differences between levels. During recovery period the shortening velocity of diaphragm, abdominal and inspiratory muscles of the rib cage returned to quiet breathing values.

4. Discussion

In our study we were able to evaluate the effects of different levels of PEP on different lung variables in Parkinson's patients. Our data showed that Parkinson's patients show less efficient breathing pattern when compared to controls as it can be observed by the decreased tidal volume and increased respiratory rate showed by these patients. Although the decreased V_t showed by these patients we found that the use of different levels of PEP was able to increase chest wall volume when compared to quiet breathing. The

distribution of ΔV_{CW} among its compartments also varied between the groups with the controls showing a more homogenous distribution compared to Parkinson's. Another important finding is that respiratory muscles strength was also lower in Parkinson's when compared to controls. Respiratory cycle time also differed significantly between the groups. Regarding operational volumes, Parkinson's patients exhibited lower values of EIV and higher values of EEV compared to controls. Shortening velocity also showed different pattern between the groups during PEP levels.

One possible explanation for the lower tidal volume showed in Parkinson's is mainly related to a rigid pulmonary rib cage compartment. Thus, the less effective effects of PEP in Parkinson's are mostly due to pulmonary rib cage restriction and inspiratory muscle strength decrease. Moreover, we were able to confirm that Parkinson's patients show a mild restrictive pattern characteristic when compared to healthy subjects. A previous study (Sabaté et al., 1996) has related this pattern to posture alterations as limited trunk flexion, which changes the spinal axis, and thoracic mobility, with

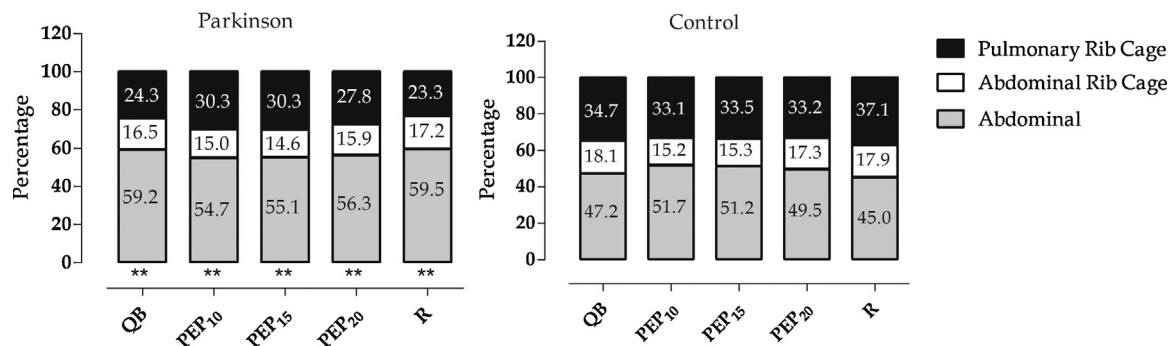


Fig. 3. Effects of PEP on compartmental distribution of tidal volume. QB: quiet breathing. R: recovery. **Intergroup differences, $p < 0.01$.

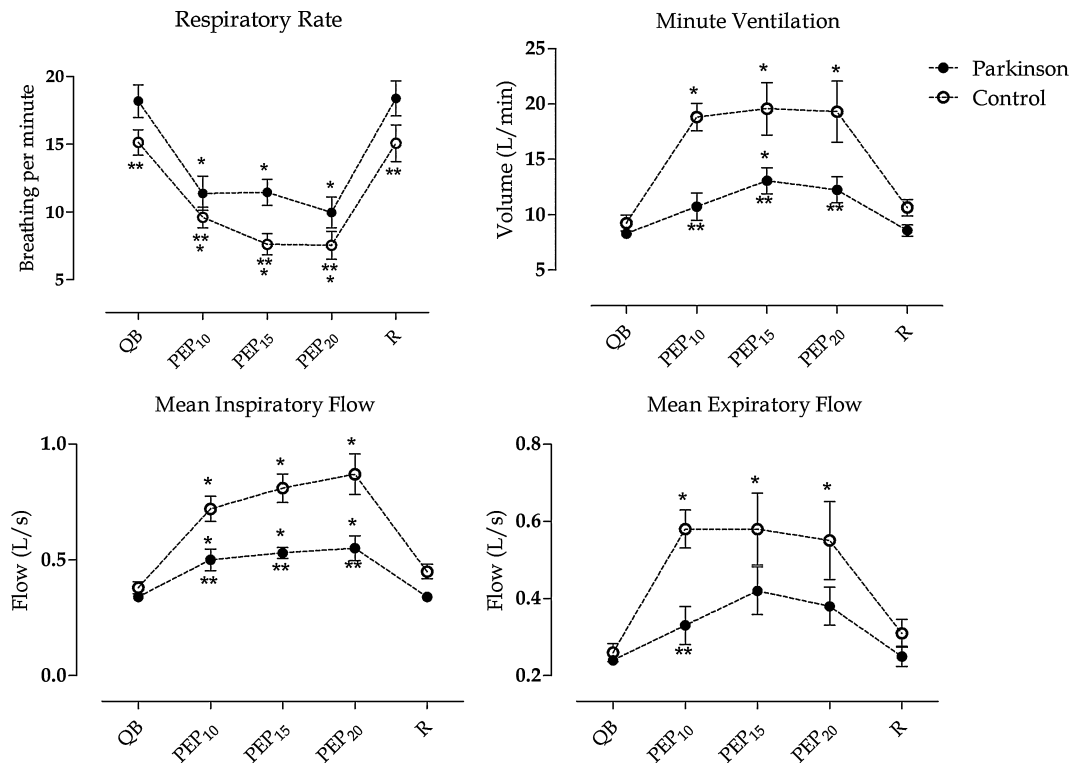


Fig. 4. Effects of PEP on total respiratory rate, minute ventilation mean of inspiratory and expiratory flow. QB: quiet breathing. R: recovery. *Intragroup difference comparing quiet breathing, $p < 0.05$. **Intergroup differences, $p < 0.05$.

a thoracic motion range reduction which culminates in a decrease of respiratory system complacency.

Sande de Souza et al. (2011) performed a study in which they evaluated 10 patients with Parkinson's disease to 9 healthy subjects by electromyographic analysis and found that, low velocity is caused by low electromyographic activity and difficulty in modulating explosive muscle power. Tremor was the signal that dominated muscle activity, and it results from muscle contraction with irregular activation of motor units, which is considered an

important factor for muscle weakness. According to our results, it may be hypothesized that the same pattern repeats itself in Parkinson's respiratory muscles.

The use of PEP led to an increase of tidal volume in Parkinson's patients. Abdominal compartment accounted for more than half of this volume in these patients. Based on the fact that we did not find any difference between the three levels of PEP we suggest that a level of 10 cmH₂O is able to reach important physiological changes in this group. The different results observed in healthy controls may

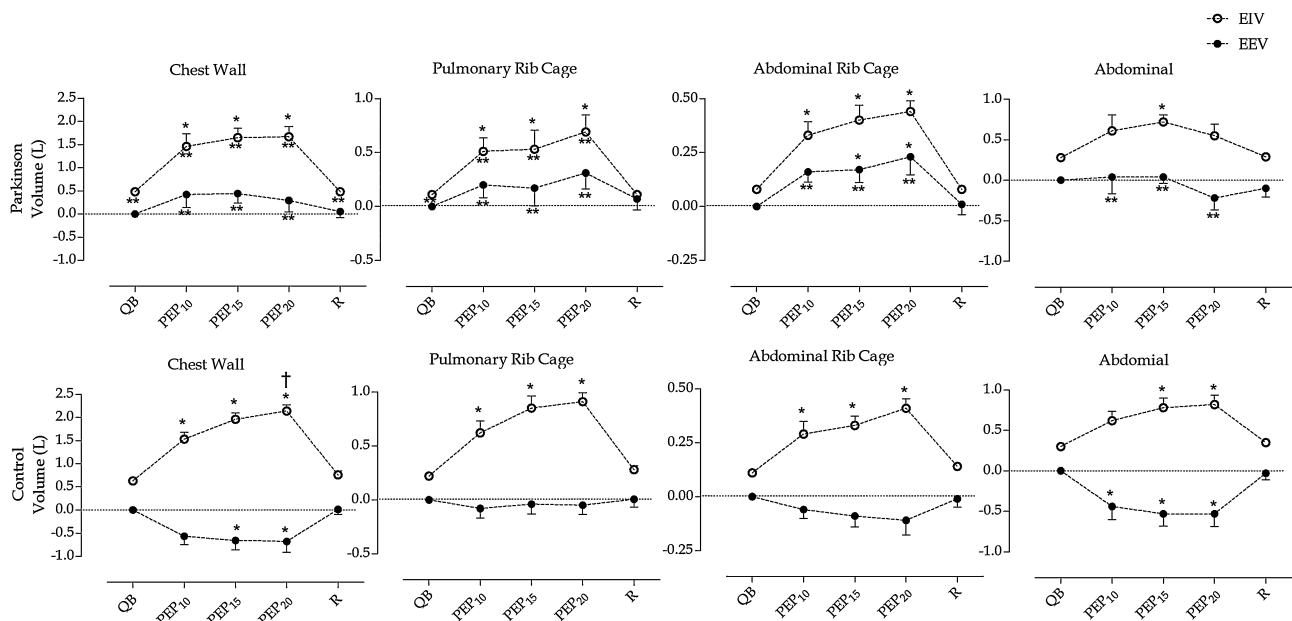


Fig. 5. Effects of PEP on operational volume of chest wall and its compartments in Parkinson's and controls. QB: quiet breathing. R: recovery. *Intragroup difference comparing quiet breathing, $p < 0.05$. †Intragroup difference comparing PEP₁₀, $p < 0.05$. **Intergroup differences, $p < 0.05$.

be related to rib cage restriction absence and preserved respiratory muscle strength.

Furthermore, we may attribute greater activity in the abdominal compartment to restricted thoracic mobility in Parkinson's patients. Our finding differs from those reported by Parreira et al., 2003, which compared the contribution of rib cage and abdomen compartments to the tidal volume of 10 patients with Parkinson's in the "ON" condition and 10 healthy individuals, by respiratory inductance plethysmography. The study did not find significant difference for abdominal compartment contribution between Parkinson's patients and healthy subjects during quiet breathing even with Parkinson's showed higher absolute values. Differences between the studies may be related to the type of equipment used in their investigation. Electrical inductance plethysmography seems to be less accurate and is based in two degrees of freedom to assess chest wall and its compartments movements. Thus, its capacity and accuracy is significantly different from OEP.

Differences in respiratory cycle time may be due to Parkinson's breathing pattern, which is characterized as superficial with shorter total respiratory cycle time, inspiratory time and expiratory time compared to healthy individuals. Respiratory rate was reduced in Parkinson's patients at all PEP levels without differences between them. Thus, we suggest that the use of 10 cmH₂O would be sufficient to reach physiological changes that would improve breathing pattern in Parkinson's.

The end-expiratory volume in patients with Parkinson's was slightly higher after the use of PEP in contrast to healthy individuals, who exhibited negative variation and lung deflation with PEP₁₅ and PEP₂₀. We believe that the lack of significant increase of EEV after the use of different levels of PEP in CF subjects is due to the small sample size of our study. Regarding controls, which showed even decreased EEV values after the use of PEP in comparison to QB, we may speculate that PEP was not able to produce hyperinflation in these subjects. PEP therapy caused modifications in Parkinson's patients, different from that observed in other pathologies, where the use of PEP promotes pulmonary hyperinflation (Dellaca et al., 2001).

One hypothesis to explain differences between shortening velocity pattern is related to the lower respiratory muscle strength and lesser motor unit activation (synchronization) in Parkinson's along with less rib cage mobility.

Based on our findings it is possible to conclude that Parkinson's subjects exhibit important alterations in different breathing pattern components and that the use of PEP has significant physiological effects on breathing pattern and chest wall volumes even with 10 cmH₂O.

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