Respiratory Physiology & Neurobiology 259 (2019) 63–69

Contents lists available at ScienceDirect

Respiratory Physiology & Neurobiology

journal homepage: www.elsevier.com/locate/resphysiol

Pulmonary rehabilitation and BDNF levels in patients with chronic obstructive pulmonary disease: A pilot study

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ARTICLE INFO

Keywords:
Exercise training
Endurance training
Resistance training
Respiratory health

ABSTRACT

Background: COPD physiopathology involves multiple pathways and evidence indicates that brain-derived neurotrophic factor (BDNF) is an important biomarker associated with parameters of COPD severity. This study aimed to analyze the time course of the effects of a pulmonary rehabilitation program (PRP) on BDNF levels and on functional status in COPD patients.
Methods: Patients were enrolled in a 24-session PRP. Exercise capacity, dyspnea, health-related quality of life, and the BODE index were assessed at baseline and after the PRP. BDNF plasma levels were measured at baseline (immediately before the 1st session), after the 1st session, and before and after the 24th session.
Results: Sixteen patients were included. A reduction in BDNF levels was observed after the 1st session and an increase was observed between the end of the 1st session and the beginning of the 24th session. The PRP promoted an improvement in exercise capacity and health-related quality of life and a reduction in dyspnea and the BODE index.
Conclusion: Exercise acutely reduced BDNF levels, an effect that was nullified by the overall intervention.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by airflow limitation with persistent respiratory symptoms and systemic manifestations and is considered the fourth leading cause of death worldwide. Patients with COPD present with pulmonary function impairment, dyspnea, and peripheral muscle dysfunction, contributing to exercise intolerance and reduced activitiesof daily living (Vogelmeier et al., 2017). Moreover, patients with COPD show a high prevalence of psychiatric symptoms (*e.g.*, depression), which are pointed out as relevant comorbidities in these individuals (Coventry, 2009).

The pathophysiology of COPD involves multiple pathways such as the activation of circulating inflammatory cells and increased levels of proinflammatory cytokines (Agustí et al., 2003; Rahman et al., 1996) and the imbalance of epigenetic markers (Zong et al., 2015; Schamberger et al., 2014), which have been shown to be modulated by exercise (da Silva et al., 2017). Emerging experimental and clinical evidence indicates that brain-derived neurotrophic factor (BDNF) is an important biomarker in COPD, with higher peripheral levels when compared to a control group (Pinto-Plata et al., 2007; Stoll et al., 2012).

BDNF is a neurotrophin associated with several processes such as neuroplasticity and neuronal growth, differentiation, and repair (McAllister et al., 1999). Furthermore, it appears to play a major role in cognition, emotion, and mood and it is related to the pathophysiology of several diseases including neuropsychiatric conditions (Karlovic et al., 2013; Binder and Scharfman, 2004). Although found throughout

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https://doi.org/10.1016/j.resp.2018.07.011
Received 26 February 2018; Received in revised form 7 July 2018; Accepted 29 July 2018
Available online 29 July 2018
1569-9048/

the brain, BDNF can cross the blood-brain barrier in a bi-directional manner, and peripheral levels seem to present a strong correlation with cerebrospinal fluid levels (Pan et al., 1998). Therefore, peripheral BDNF levels have been used as a biomarker in several clinical studies (Schuch et al., 2015; Erickson et al., 2012).

Despite these findings regarding brain function, the role and regulation of BDNF in COPD is not yet fully understood. It has been proposed that this neurotrophin plays a pivotal role in acute and chronic inflammatory conditions of the airways. Specifically, it can enhance the number and function of airway smooth muscle cells (Aravamudan et al., 2012) and is involved in airway hyperresponsiveness and cough (Lommatzsch et al., 2007, 2005). Elderly patients with COPD have higher levels of this neurotrophin when compared with age-matched controls (Loza et al., 2012). In addition, Pinto-Plata and colleagues (Pinto-Plata et al., 2007) reported that BDNF correlated with forced expiratory volume in one second (FEV_1), carbon monoxide transfer factor, performance in the six-minute walk test (6MWT), BODE index, and frequency of exacerbation.

A pulmonary rehabilitation program (PRP) is an important strategy for promoting beneficial effects in COPD patients. It consists of a multidisciplinary intervention that includes mainly exercise training and educational sessions to help patients recover independence and functional capacity (Spruit et al., 2013). Several studies have reported that COPD patients submitted to a PRP show improvements in exercise capacity and health-related quality of life as well as reductions in dyspnea and frequency and duration of hospitalizations (Spruit et al., 2013).

In this context, one can question the effect of exercise on BDNF levels in patients with COPD. While higher BDNF levels seem to be associated with a more severe impact of COPD (Pinto-Plata et al., 2007), there is a growing body of evidence reporting that different training protocols can decrease psychiatric symptoms in both healthy and patient populations by engaging BDNF upregulation (Heyman et al., 2012; Krogh et al., 2014; Schuch et al., 2014). However, no studies have investigated the effects of a PRP on BDNF levels in patients with COPD. Therefore, this study aimed to analyze the acute and overall effects of a PRP on BDNF levels and investigate the impact of this PRP on exercise capacity, health-related quality of life, dyspnea, and the BODE index in COPD patients.

2. Methods

Patients with COPD confirmed by spirometry (GOLD stages 2, 3, and 4 of the severity of airflow limitation (Vogelmeier et al., 2017)) were recruited from the Pulmonology Service of Irmandade da Santa Casa de Misericórdia de Porto Alegre (ISCMPA), Porto Alegre, RS, Brazil. Subjects should be clinically stable in the four weeks before the study protocol, nonsmokers for at least six months with a smoking history ≥ 20 pack-years, and aged 40 years and over. The exclusion criteria were self-reported current smoking, oral corticosteroid use, participation in any exercise program in the last 12 months, pulmonary disease other than COPD or other diseases such as musculoskeletal, neurologic, or cardiovascular that would compromise their ability to perform any of the evaluations in the study. Subjects were classified as frequent exacerbator if they presented at least two exacerbations or at least one exacerbation leading to hospital admission. Inclusion and exclusion criteria were assessed by both interview and medical records. At baseline, subjects were assessed for depression with the Beck Depression Inventory (BDI). Exercise capacity, dyspnea, and health-related quality of life were assessed on the same day, two to four days before the beginning of the intervention, and two to four days after the last PRP session.

This study was approved by the Human Research Ethics Committee of ISCMPA (protocol no. 40078114.9.0000.5335) and Centro Universitário Metodista-IPA (protocol no. 918.889/2014), and all subjects provided written informed consent. The current study has been registered at the Brazilian Clinical Trials Registry (Registro Brasileiro de Ensaios Clínicos - ReBEC) under number RBR-26pms3.

2.1. Pulmonary function test

Data on lung function were collected from medical records no later than six months prior to protocol. All tests were performed before and after bronchodilator inhalation at the Pulmonary Function Laboratory of ISCMPA according to the recommendations of the American Thoracic Society (ATS)/European Respiratory Society (ERS) (Miller et al., 2005). The equation proposed for the Brazilian population was used to calculate the predicted values (Pereira et al., 2007).

2.2. Depression

The BDI (Gorenstein and Andrade, 1996) was used to assess depression. It is a self-administered inventory that consists of 21 items related to depressive symptoms and attitudes that can be rated from 0 to 3 as to intensity, resulting in a total score that can range from 0 to 63 points. Levels of depression are classified as minimum depression (0–11), mild depression (12–19), moderate depression (20–35), or severe depression (36–63).

2.3. BDNF measurement

To analyze the acute and overall effects of a PRP on BDNF levels, blood samples (approximately 5 ml) were taken from the antecubital vein of individuals at different time- points: baseline, immediately after the 1st PRP session, and before and immediately after the 24th session. All blood samples taken before the sessions were taken after the subjects had rested for 10–15 min, and the samples taken after the sessions were taken no more than five minutes after the end of the sessions. The blood samples were centrifuged, and the plasma was stored at -20 °C until analysis.

Plasma BDNF levels were determined by the ELISA method (Sigma-Aldrich commercial kit; catalog number RAB0026) according to manufacturer instructions. Briefly, the sample and BDNF specific standards were added to the ELISA microplate and incubated for 2.5 h at room temperature. Subsequently, the solutions were discarded, and the same plate was washed four times with wash buffer (PBS, Tween 20 0.01%). After washing, the secondary antibody bound to biotin was added and incubated for 1 h at room temperature with gentle agitation. The plate was again washed with wash buffer, a streptavidin solution was added, and the plate was incubated at room temperature for 45 min with gentle agitation. The solution was discarded, and the plate passed through the washing process. Tetramethylbenzidine was added, then plate was incubated for 30 min at room temperature, light deprivation, with gentle agitation. The stop solution was added, and finally the plate was read in a spectrophotometer at a wavelength of 450 nm. The plasma BDNF levels were expressed as ng/ml.

2.4. Exercise capacity

Exercise capacity was assessed using the six-minute walking test (6MWT) conducted according to the recommendations of the ERS/ATS (Singh et al., 2014). Two tests were performed with a 30-minute interval and the best performance was used for the analysis. Reference values were calculated according to the reference equation for the Brazilian population (Britto et al., 2013).

2.5. Dyspnea

Dyspnea was assessed with the modified Medical Research Council (mMRC) scale that rates the degree of dyspnea on activities of daily living. Scores range from 0 to 4, and the maximum score indicates greater dyspnea (Kovelis et al., 2008).

2.6. Health-related quality of life

Health-related quality of life was assessed using the St. George Respiratory Questionnaire (SGRQ), a disease-specific questionnaire, validated in Brazil (Camelier et al., 2006). The SGRQ consists of three domains (symptoms, activity, and impact of disease) divided into 76 items with scores from 0 to 100. The highest score is indicative of poor quality of life in any one of the domains in total calculation. Values above 10% reflect impaired quality of life in that domain or the total score.

2.7. BODE index

The body mass index (B), degree of obstruction (O), perception of dyspnea (D) and exercise capacity (E) index (BODE index) is a multidimensional grading system that predicts the risk of death from any cause and from respiratory causes among patients with COPD. The BODE index was calculated as previously described by Celli and Cote (Celli et al., 2004), and its score goes from 0 to 10 divided into quartiles. The higher quartile means higher risk of death.

2.8. Pulmonary rehabilitation program (PRP)

Patients took part in a supervised 24-exercise training program designed according to the ATS and the ERS (Spruit et al., 2013). The protocol involved endurance training and peripheral mucle training three times per week (approximately 90 min each session). The endurance training was performed on a treadmill with 30 min of load initially determined at 60% of the average speed in the 6MWT. The work load progression followed the dyspnea report (4–6 on the modified Borg scale (Borg, 1982)). The lower limb training involved quadriceps and triceps surae with free weights and/or on the extension machine (two sets of 10–15 repetitions). The upper limb training was carried out in diagonal axes with free weights or elastic bands, and each diagonal was performed in two sets, lasting two minutes each. In addition, patients received nutritional guidance and educational orientation regarding disease self-management.

2.9. Statistical analysis

Normal distribution was checked using the Shapiro–Wilk test. Data were reported as mean (SD), 95% confidence interval (CI95%), or median (25–75% interquartile range). The Generalized Estimating Equations (GEE) with Bonferroni post hoc analysis, considering the Gamma model, was used to compare BDNF levels at baseline (immediately before the first session), immediately after the first session, immediately before the 24th session, and immediately after the 24th session. GEE was also performed correcting the data for age, sex, smoking history, BDI score, and use of antidepressant medication. Changes in data regarding exercise capacity, health-related quality of life, and depression were assessed using the Wilcoxon test. Comparisons between frequent exacerbators and non-frequent exacerbators were tested with Mann-Whitney's U test. Correlations were tested with the Spearman test. Statistical significance was set at $p < 0.05$. Data were analyzed using SPSS 20.0 (SPSS, Chicago, IL, USA), and the graph was made with GraphPad Prism 6 (GraphPad Software Inc., La Jolla, CA, USA).

3. Results

Twenty patients took part in the study and sixteen completed the intervention (two deaths and two withdraws). All 16 patients successfully performed 24 PRP sessions. Six subjects presented minimum depression, seven presented mild depression, and three presented moderate depression. However, six subjects were taking antidepressant medication. Subjects characteristics are shown in Table 1.

Table 1
Participant characteristics (n = 16).

Characteristics	Mean ± SD
Age, years	68.5 (6.7)
Male/female, n	9/7
Frequent exacerbator, n	8
Smoking history, pack-years	60.1 (31.4)
Tobacco abstinence, years	12.4 (6.4)
FEV_1, l	1.06 (0.44)
FEV_1, %pred	39.0 (14.0)
FVC, l	2.17 (0.71)
FVC, %pred	60.1 (12.0)
FEV_1/FVC, %	0.48 (0.08)
BMI, kg/m^2	25.1 (4.9)
BDI, score	13 (11 – 17)

Data given as frequency (n), mean (standard deviation), or median (25–75% interquartile range). FEV_1: forced expiratory volume in one second, in liters; FVC: forced vital capacity, in liters; %pred: percent of the predicted value; BMI: body mass index, weight/height^2; BDI: Beck Depression Inventory.

The BDNF levels at baseline (before the first PRP session) and before the 24th session did not correlate with the BDNF levels at baseline and post PRP for BDI score, exercise capacity, health-related quality of life, dyspnea, BODE index, or pulmonary function ($p > 0.05$).

Exercise capacity, dyspnea, BODE index (score and quartile), and SGRQ total score and activities domain improved significantly after the PRP intervention compared to baseline (Table 2). The body mass index did not change after the PRP [25.1 (4.2) *vs.* 25.1 (4.5) kg/m^2; p = 1.0].

Post hoc analysis revealed a reduction in BDNF levels after the 1st session compared to baseline ($p < 0.001$; Cohen's D effect size of 1.19) and increase between the end of the 1st session and beginning of the 24th session ($p < 0.001$; Cohen's D effect size of 1.01). No significant difference was found between baseline, the beginning of the 24th session, and the end of the 24th session (Fig. 1). Age, sex, smoking history, and BDI score did not influence the results (Table 3). The use of antidepressant medication seems to influence BDNF levels (p = 0.008), but the change in BDNF levels remained the same regardless of the use of antidepressants.

The change in BDNF levels in the first session was inversely correlated with its levels at the beginning and the end of the session (Fig. 2). However, the change in BDNF levels in the first session was not correlated with exercise capacity, health-related quality of life, dyspnea, the BODE index, or pulmonary function ($p > 0.05$).

Table 2
Effects of exercise-based PRP on clinical outcomes.

Characteristics	Baseline	After PRP	p
Exercise Capacity (6MWT, m)	416.0 (76.5)	480.4 (84.8)	0.003
Exercise Capacity (6MWT, % pred)	74.1 (65.4 – 87.7)	87.7 (76.7 – 97.9)	0.003
Dyspnea (mMRC)	4.0 (2.3 – 4)	2.0 (1.3 – 3)	0.011
Bode index, score	4.81 (1.91)	4.06 (1.53)	0.012
Bode index, quartile	3.0 (2.0 – 3.0)	2 (2.0 – 3.0)	0.008
SGRQ total score	53.9 (40.8 – 64.6)	49.1 (35.7 – 51.4)	0.007
SGRQ Symptoms	52.0 (22.7)	40.2 (21.9)	0.069
SGRQ Activities	77.6 (13.9)	64.5 (16.2)	0.005
SGRQ Impact	38.8 (17.1)	31.6 (12.0)	0.070

Data shown as mean (standard deviation) or median (25–75% interquartile range). Baseline: immediately before the first session; After PRP: immediately before the 24th session; Exercise capacity: distance walked during the six-minute walking test (6MWT) in meters and in percentage of the predicted value (%pred); Dyspnea: score of the perception on the modified Medical Research Council (mMRC); BODE index: score and quartile of the body mass index (B), degree of obstruction (O), perception of dyspnea (D), and exercise capacity (E) index; SGRQ: scores of the Saint George Respiratory Questionnaire.

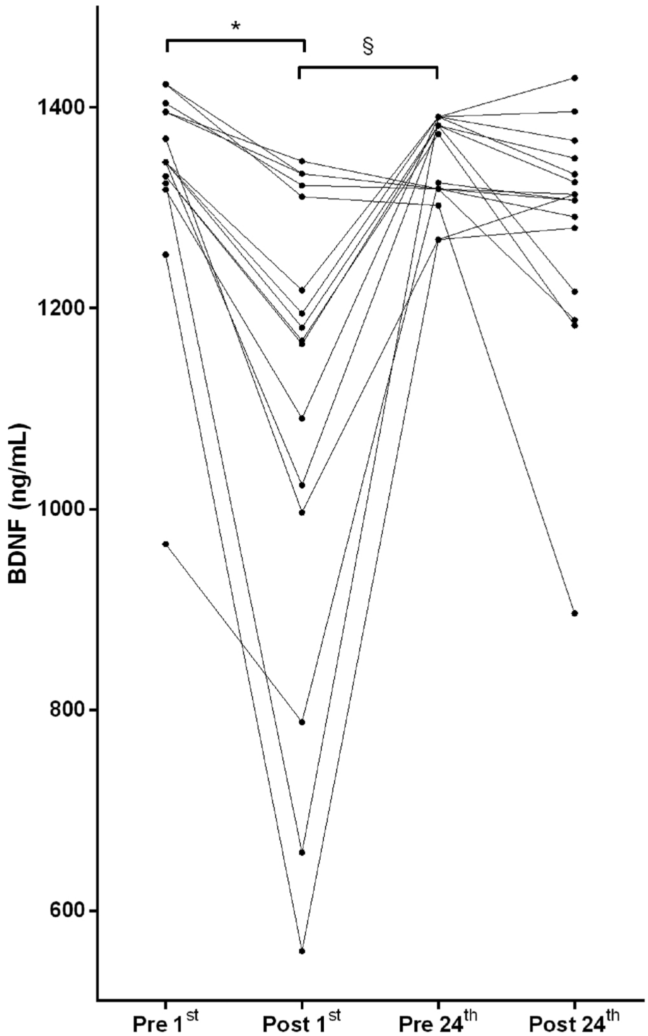

Fig. 1. Effect of exercise-based PRP on plasmatic BDNF levels.
BDNF: Brain-derived neurotrophic factor. Plasmatic BDNF levels at baseline immediately before the first session [Pre 1st; 1332.2 (104) ng/mL, CI95% 838.4–2116.7]; immediately after the first session [Post 1st; 1105.4 (237.6) ng/mL, CI95% 673.8–1813.4]; immediately before the 24th session [Pre 24th; 1345.1 (43.2) ng/mL, CI95% 848.3–2132.9]; and immediately after the 24th session [Post 24th; 1281.2 (118.9) ng/mL, CI95% 807.5–2032.8].
* Reduction in BDNF levels when compared to the beginning of the first session (acute effect); $p < 0.001$.
§ Increase in BDNF levels when compared to the end of the first PRP session; $p < 0.001$ (GEE followed by Bonferroni's post hoc).

Baseline characteristics and the acute and overall effects of the PRP did not differ between frequent and non-frequent exacerbators.

4. Discussion

The present study investigated for the first time the effects of an exercise-based PRP on BDNF levels in patients with COPD. Specifically, our results showed a significant reduction in this neurotrophin after the first training session compared to baseline. However, this acute effect was nullified in response to the overall PRP intervention. As expected, the current study also demonstrated the beneficial impact of a PRP on health-related quality of life, dyspnea, and exercise capacity, as well as risk of death measured by the BODE index.

The literature is divergent regarding the acute and chronic effects of exercise on BDNF levels. Several studies showed acute increases in BDNF after a single bout of endurance exercise in healthy subjects (Seifert et al., 2010; Mang et al., 2014; Kawazu et al., 2016; Gold et al., 2003; Saucedo Marquez et al., 2015), while others showed no change (Castellano and White, 2008; Strohle et al., 2010; Zoladz et al., 2008). Conflicting evidence also exists regarding the chronic impact, with at least two studies showing an increase after endurance training (Seifert et al., 2010; Zoladz et al., 2008), while others reported that neither endurance training (Castellano and White, 2008; Schiffer et al., 2009) nor resistance training Schiffer et al., 2009; Levinger et al., 2008) alters this neurotrophin. It is important to point out that the PRP included both endurance training (treadmill) and resistance training (weight resistance). In fact, endurance and resistance training may have different effects on BDNF levels, especially when combined.

Table 3
BDNF levels adjusted according to the subject's characteristics.

Factor / covariable	BDNF, ng/mL				p	r^2
	Pre 1st	Post 1st	Pre 24th	Post 24th		
Antidepressant					0.122	0.305
No	1356.4 (35.14)	1167.6 (187.9)	1365.6 (31.01)	1329.5 (63.27)		
Yes	1291.9 (155.5)	1002.1 (273.2)	1310.8 (38.74)	1200.2 (143.5)		
Sex					0.401	0.267
Male	1312.9 (127.1)	1092.6 (217.8)	1362.6 (29.88)	1301.7 (61.88)		
Female	1357.1 (53.28)	1122.2 (260.0)	1322.6 (47.11)	1254.5 (161.8)		
Age, years	1332.2 (4570.0)	1105.5 (3887.4)	1345.1 (4610.3)	1280.4 (4404.4)	0.190	0.320
Smoking history, pack-years	1332.2 (3729.8)	1105.4 (3063.7)	1345.1 (3728.2)	1281.2 (3569.9)	0.676	0.306
BDI, score	1332.2 (1258.9)	1105.4 (1116.7)	1345.1 (1265.5)	1281.2 (1207.0)	0.813	0.305

Data shown as mean (standard deviation). Pre 1st: immediately before the first session; Post 1st: immediately after the first session; Pre 24th: immediately before the 24th session; Post 24th: immediately after the 24th session; p: significance of the interaction between BDNF levels and the factor/covariable in the GEE; r^2 : coefficient of determination; BDI: Beck Depression Inventory.

Similar to our experimental design, other studies have also investigated the time course of BDNF levels in response to exercise. Yarrow and colleagues (Yarrow et al., 2010) showed, in healthy young men, that endurance exercise acutely increases serum BDNF levels at baseline and after five weeks, demonstrating both acute and chronic changes. In addition, Castellano et al. (Castellano and White, 2008) reported no changes in BDNF levels 30 min after an endurance exercise session in patients with multiple sclerosis, while BDNF levels decreased after two hours resting, remaining decreased up to three hours after the exercise session. Interestingly, the authors showed that BDNF remains unchanged eight weeks after the intervention, suggesting an adaptation following chronic exposure. Thus, these data led us to hypothesize that different from healthy individuals, in patients with chronic diseases such as COPD and multiple sclerosis, BDNF modulation seems to occur in a time-dependent manner, changing only acutely in response to exercise and reaching homeostasis as an adaptation to exercise training.

According to Yarrow and colleagues (Yarrow et al., 2010), the acute reduction in BDNF levels may also suggest (1) a greater tissue uptake and/or binding with tropomyosin-related kinase receptors in central and peripheral tissues, (2) greater clearance of BDNF from circulation, and/or (3) reduced secretion of BDNF during recovery. Meanwhile, further studies are necessary to investigate the early-phase effects of training on BDNF levels in COPD patients.

Several physiological mechanisms may be behind the regulation of BDNF. The brain appears to be the largest source of BDNF in exercise (Rasmussen et al., 2009). In addition, the vascular endothelium cells also synthesize and secrete BDNF (Nakahashi et al., 2000) and cardiovascular adaptations to exercise may be an influence on the regulation of this neurotrophin.

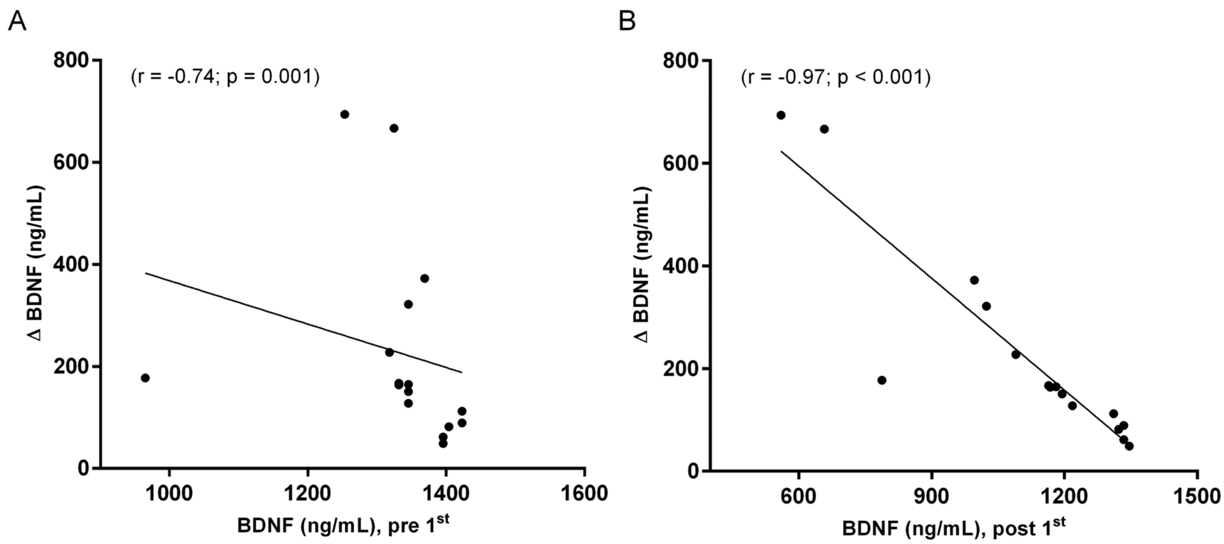

Fig. 2. Correlations between plasmatic BDNF levels and the acute effect of the PRP.
BDNF: Brain-derived neurotrophic factor. A: Correlation between the change in plasmatic BDNF levels at the first session and the BDNF levels at baseline (immediately before the first session). B: Correlation between the change in plasmatic BDNF levels in the first session and the BDNF levels immediately after the first session.

It has been proposed that BDNF is stored in platelets and released from the platelets under inflammatory environments (Fujimura et al., 2002). However, we recently showed that a single PRP session did not change peripheral inflammatory markers (da Silva et al., 2017). Interestingly, there is growing evidence demonstrating a suppression of BDNF production by corticosteroids (Lommatzsch et al., 2005, 2004). Therefore, an important feature that may explain the sharp reduction in peripheral BDNF levels after exercise found in the current study could be the increase in cortisol levels after physical stress, since cortisol seems to inhibit BDNF (Murakami et al., 2005; Issa et al., 2010; Mondelli et al., 2011). Nevertheless, the interaction of cortisol with BDNF in patients with COPD needs to be clarified, considering their chronic use of inhaled corticosteroids.

While platelets are considered the main source of circulating BDNF (Nakahashi et al., 2000; Huang et al., 2014; Tang et al., 2008), monocytes and activated T and C lymphocytes are considered secondary sources (Kerschensteiner et al., 1999). In this context, a single training session in previously sedentary COPD patients may change their immunological profile, which may be related to the acute exercise effect in sedentary patients with COPD.

As previously described, BDNF plays a significant role in acute and chronic inflammatory conditions of the airways. Previous studies (Pinto-Plata et al., 2007; Stoll et al., 2012) showed that patients with COPD present elevated BDNF levels when compared to matched controls. In fact, BDNF is believed to induce neuronal hyperreactivity leading to hyperresponsiveness and cough (Lommatzsch et al., 2007, 2005) and to increase quantity and function of airway smooth cells (Aravamudan et al., 2012), considering a marker of neuromuscular dysfunction of the airways. In addition, in a previous study, higher BDNF levels were associated with worse lung function, exercise capacity, and mortality risk (Pinto-Plata et al., 2007) and might be related to the SGRQ Impact score (Papp et al., 2017) in patients with COPD. Airway changes induced by exercise, such as bronchial hyperreactivity and dynamic hyperinflation, may be a regulatory mechanism for BDNF. Nonetheless, PRP induced changes in exercise capacity, quality of life, and risk of death (assessed by the BODE index) without changing the BDNF levels.

BDNF seems to be a potential biological moderator of antidepressant response (Shimizu et al., 2003), and evidence shows that exercise increases the levels of this neurotrophin in depressed subjects (Heyman et al., 2012; Krogh et al., 2014; Schuch et al., 2014). In the present study, however, the BDI score did not influence the results while the use of antidepressant medication did. Despite this, the effects of exercise on BDNF levels remained the same, even adjusting the data regarding antidepressant medication use. It is also important to emphasize that the current sample did not present with major depression. Nevertheless, anxiety was not assessed and may have been a factor influencing BDNF levels (Suliman et al., 2013), since anxiety may decrease with chronic exercise (Tselebis et al., 2013).

Another important finding of the current study is that the lower the BDNF level is, the higher the change induced by the first PRP session will be. Although we did not find a correlation between any of the clinical features assessed in the current study, this finding reinforces the hypothesis of previous studies that BDNF may be a marker for disease severity and impact (Pinto-Plata et al., 2007; Stoll et al., 2012; Papp et al., 2017) and even for treatment responsiveness. The physiological relevance of this findings in COPD individuals must be investigated in future studies.

We acknowledge that the current study has some limitations such as the lack of a control group, the small sample size, and the high variability in the acute effect of the PRP on BDNF levels. All care was taken with regard to the time of collection and storage of blood for biochemical tests. Even though this was a pilot study with a small sample size, we found a statistical power of 93.6% in the acute effect of the PRP on BDNF levels. On the other hand, the sample size was not sufficient to demonstrate the chronic effect of the PRP on BDNF levels and its correlations between clinical parameters. Pulmonary rehabilitation has enough evidence to support our findings regarding exercise capacity, health-related quality of life, and risk of death in patients with COPD. Another possible limitation was the lack of control of caffeine and alcohol intake, which could influence BDNF levels (Logrip et al., 2009; Moy and McNay, 2013; Costa et al., 2008). However, none of the subjects were alcoholics. Nevertheless, it is important to reinforce that this is a real-time prospective study.

5. Conclusions

In summary, exercise acutely reduced BDNF levels, but this effect was nullified by the overall intervention. In addition, our study supports the evidence that pulmonary rehabilitation improves exercise capacity, health-related quality of life, and the BODE index in COPD patients. However, these beneficial effects are not linked to BDNF regulation, since this neurotrophin is able to respond uniquely in an acute way (single session). We might propose an exercise adaptation-related change in the BDNF dose–response, however further studies are needed for a better understanding of the BDNF modulation pathways in individuals with COPD.

Funding source/trial registration

This study was partially supported by the Brazilian National Council for Scientific and Technological Development (CNPq), the Foundation for Research Support of Rio Grande do Sul State (FAPERGS), and the Fleury Group. This study is registered at www.ensaiosclinicos.gov.br (No. RBR-26pms3).

Acknowledgements

The authors wish to thank those who helped with data acquisition and the Fleury Group for their assistance.

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