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RESEARCH ARTICLE

Whole body vibration training increases physical measures and quality of life without altering inflammatory-oxidative biomarkers in patients with moderate COPD

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Neves CD, Lacerda AC, Lage VK, Soares AA, Chaves MG, Lima LP, Silva TJ, Vieira ÉL, Teixeira AL, Leite HR, Matos MA, Mendonça VA. Whole body vibration training increases physical measures and quality of life without altering inflammatory-oxidative biomarkers in patients with moderate COPD. *J Appl Physiol* 125: 520–528, 2018. First published May 3, 2018; doi:10.1152/japplphysiol.01037.2017.—Whole body vibration training (WBVT) has been identified as an alternative intervention to improve exercise capacity and quality of life of patients with chronic obstructive pulmonary disease (COPD). However, the effect of WBVT on inflammatory-oxidative biomarkers remains unknown. The aim of this trial was to investigate the effects of WBVT on quality of life and physical and inflammatory-oxidative parameters in patients with COPD. Twenty patients were equally divided into *1*) an intervention group (IG) that performed the WBVT, and *2*) a control group (CG) that did not receive any intervention. Intervention consisted in performing static squatting on a vibrating platform, in six series of 30 s, 3 days/wk, for 12 wk. Patients were evaluated for plasma levels of IL-6, IL-8, IFN-γ, soluble receptors of TNF-α; white cell count; plasma levels of oxidant and antioxidant markers; 6-min walking distance (6MWD); peak oxygen uptake ($\dot{V}O_{2peak}$); handgrip strength; quality of life; timed 5-chair sit-to-stand (5STS); and timed get-up and go test (TUG). After WBVT, patients from IG showed a significant increase in the 6MWD, $\dot{V}O_{2peak}$, and handgrip strength ($P < 0.05$). Furthermore, patients from the IG reached minimal clinically important difference regarding quality of life. No significant differences were found in 5STS, TUG, inflammatory-oxidative biomarkers, and white cell count in the IG. The CG did not show significant improvement in all assessments ($P > 0.05$). Taken together, our results demonstrated that the WBVT induced clinically significant benefits regarding exercise capacity, muscle strength, and quality of life in patients with COPD that were not related to inflammatory-oxidative biomarker changes.

NEW & NOTEWORTHY Whole body vibration training is a new option for nonpharmacological treatment of chronic obstructive pulmonary disease (COPD). This study showed the potential of this training to improve exercise capacity, quality of life, and muscle strength in patients with COPD. Furthermore, to our knowledge this was the first study showing that vibration exercise does not modify the plasma levels of inflammatory-oxidative biomarkers, suggesting that the beneficial effects on physical measures and quality of life are independent of changes in biomarkers.

COPD; exercise capacity; handgrip strength; quality of life; vibration exercise

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common, preventable, and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation (21a). The chronic airflow limitation is associated with airway and/or alveolar abnormalities, caused by chronic inflammation of small airways and lung parenchyma (21a).

Regarding the inflammatory response involved in COPD it is important to highlight the inflammatory mediators, mainly interleukin (IL)-8 (attracts neutrophils and monocytes), interferon gamma (IFN-γ) (strong amplifier of CD8+ T lymphocytes activation), IL-6 (pro-inflammatory and anti-inflammatory function), and tumor necrosis factor-alpha (TNF-α) (2), which has the role of attracting immune cells from the circulation. Inflammatory cells are also important sources of reactive oxygen species (ROS), and this excess of oxidants when not counterbalanced by the antioxidant defense system can amplify the inflammatory response, contributing to the appearance of pulmonary and extrapulmonary manifestations in COPD (1, 34).

The most potent currently available nonpharmacological treatment option for COPD is exercise training, a key component of integrated management of COPD (35). There is increased evidence for the use and efficacy of a variety of exercise training as part of pulmonary rehabilitation in patients with COPD, including endurance and strength training, which have been associated with improvements in symptoms, exercise tolerance, and quality of life in COPD patients (65). Despite the benefits of these training protocols, the majority of patients are not able to perform due to high levels of perceived dyspnea, fatigue, and fear of breathlessness, which in turn

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decreases physical activity engagement (36, 59, 71). Therefore, alternative exercise modalities, such as whole body vibration training (WBVT), have gained increasing interest especially in patients with advanced COPD (21, 48, 62).

Whole body vibration is an exercise training modality and rehabilitation tool performed on a vibrating platform that generates vertical sinusoidal vibrations. The oscillations are transmitted to the body and stimulate muscle spindles to produce muscle contraction reflexes in response to tonic vibration reflex (10, 13). Recent reviews suggested that WBVT is beneficial to COPD patients by improving their exercise capacity, without producing adverse effects (9, 22). Moreover, some preliminary evidence has showed that WBVT may be an effective exercise modality by improving functional performance (18), muscle strength (62), and quality of life in patients with COPD (8). However, the mechanisms related to these improvements are not well known. One area requiring such information is that of inflammatory-oxidative responses. Thus the evaluation of WBVT effects on inflammatory-oxidative biomarkers as well as the evaluation on physical and quality of life parameters associated with assessment of inflammatory-oxidative biomarkers in patients with stable COPD needs to be better clarified.

Therefore, the primary aim was to investigate the effects of WBVT on inflammatory-oxidative biomarker levels and exercise capacity in patients with stable COPD. The secondary aim was to evaluate the effects of WBVT functional performance in activities of daily living (ADLs), muscle strength, and quality of life in patients with stable COPD.

MATERIALS AND METHODS

Study design. This was a single-blind trial with a controlled parallel design developed at the Universidade Federal dos Vales do Jequitinhonha e Mucuri (Diamantina/Minas Gerais, Brazil). Patients were recruited from health centers in the local community from October 2015 to October 2016. This trial was approved by the local ethics committee (Identification No. 649.332) and registered at Brazilian Clinical Trials Registry (REBEC; RBR-3kxkzn). This study was conducted in accordance with Resolution No. 466/12 of the National Health Council and the Declaration of Helsinki. All volunteers gave written, informed consent to participate in the study.

Study population. To participate in the study the patients (men or women) met the following inclusion criteria: aged 45–80 yr old; no practice of physical exercise in the latest 3 mo; no exacerbation or hospital admission within the last 4 wk; functionally independent for ADLs; women in the postmenopausal period; no currently treatment with systemic corticosteroids; and no severe comorbidity and no contraindications (self-reported) for the use of WBVT (deep vein thrombosis, metal implants, pacemaker, epilepsy, tumors, arterial aneurysm, arrhythmia). The exclusion criteria were exacerbation during the study, relocation to a new city, initiation of other physical treatment, and noncompliance to study protocol.

Patients were allocated into two groups: an intervention group (IG) that performed the WBVT and the control group (CG), which did not receive the intervention. Patients from the CG received recommendations to maintain the routine of ADLs. These patients were accompanied remotely monthly by telephone and asked for possible occurrences or changes in the daily routine. The allocation between the groups was performed in accordance with the recruitment. First, we recruited all eligible patients for study, and all these patients were allocated for the IG. At a second time, new patients were recruited for CG composition. Patients from CG were paired with IG for age, sex, body mass index (BMI), pulmonary function, and smoking status. Thus this study was composed by convenience sample.

Both groups were assessed 1 wk before the beginning of the study and reevaluated immediately at the end of the study. All evaluations and interventions were performed at the same period of the day. The researchers that assessed the participants were not aware of the allocation of the patients into the groups.

Intervention. Intervention was performed 3 times/wk on alternate days, for 12 wk. The training protocol consisted in performing static squatting on a synchronic vibrating platform (FitVibe Excel Pro, GymnaUniphy, Belgium). Patients exercised in a squatting position with 30° of knee flexion, with their feet 28 cm apart, barefoot and with upper limbs holding the platform bars, performing six series of 30 s with 60 s of rest between each series. The vibratory stimulus was offered at amplitude of 2 mm and frequencies that progressively increased each 4 wk, beginning with 30 Hz, followed by 35 and 40 Hz. The acceleration of platform was measured by an accelerometer and the root mean squared acceleration in vertical axis was 1.45 *g* for 30 Hz and 2 mm; 1.83 *g* for 35 Hz and 2 mm; and 2.25 *g* for 40 Hz and 2 mm. All sessions of training were monitored by a physical therapist; and blood pressure, heart rate, and oxygen saturation were monitored before, during, and after the series. The training protocol was based on previous studies (8, 48).

Clinical assessments. Pulmonary function, body composition, smoking history, dyspnea, multidimensional COPD assessment, and inhalation medication were evaluated to determine patients' clinical characteristics. Pulmonary function was evaluated by spirometry for confirming COPD. The forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), and FEV_1/FVC were measured in accordance with the American Thoracic Society (ATS) and the European Respiratory Society (ERS) (40). The percentages of predicted spirometry values were calculated from published Brazilian population data (44). The classification of airflow limitation severity in COPD was based in Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria, and according to post-bronchodilator FEV_1 the patients were classified as mild to very severe (GOLD I–IV) (21a).

Body composition (weight, lean mass, fat mass, fat percentage, bone mineral density) was assessment by dual-energy X-ray absorptiometry (DEXA). The BMI and fat-free mass index (FFMI) were calculated by dividing body weight and lean mass, respectively, by height squared. The smoking history of the smoker and former subjects was determined through self-report of the number of pack-years, calculated as the number of smoked cigarettes per day/20 and multiplied by the number of years of smoking (52). Moreover, the smoking status was classified as non-smoker, former smoker, and smoker.

The degree of the dyspnea and the multidimensional COPD assessment was evaluated by modified Medical Research Council (mMRC) scale and BODE index, respectively. The mMRC scale is composed of 5 points (0–4) where the higher score indicates increased limitation imposed caused by dyspnea in ADLs (4). The BODE index is a simple and established multidimensional grading system composed by a 10-point scale (higher score indicates advanced COPD stage and a higher risk of death). It consists of BMI (B), airflow obstruction (FEV_1) (O), dyspnea (MMRC scale) degree (D), and exercise capacity (E) measured by 6-min walking distance (6MWD) in 6-min walk test (6MWT) (11). Additionally, the daily doses of inhalation medication were recorded.

Inflammatory-oxidative outcome measures. The blood was collected aseptically by puncturing the median cubital vein. The collection was performed with the patient in rest state, 1 wk before and after the end of the study. Global and differential white cell count was performed in the same day by automatized method (ABX Micros 60, Horiba, Japan). The tubes containing heparin and EDTA were centrifuged to remove cells and debris and were stored as plasma and erythrocytes aliquots at −80°C. The plasma levels of cytokines (IL-6, IL-8, and IFN-γ) were measured using the cytometric bead arrays kit

(BD Bioscience, San Jose, CA) according to the manufacturer's protocol. Samples were acquired in a FACSCanto flow cytometer (BD Bioscience) and analyzed using the FCAP array v1.0.1 software (Soft Flow). The detection limits were 1.6 pg/ml for IL-6, 1.2 pg/ml for IL-8, and 0.8 pg/ml for IFN-γ. Plasma soluble TNF-α receptors (sTNFR1, sTNFR2) levels were measured using conventional sandwich ELISA kits (DuoSet, R&D Systems, Minneapolis, MN), according to the manufacturer's instructions. The detection limits were 5.0 pg/ml for the kits.

Oxidative stress was evaluated by determining plasma levels of lipid peroxidation products [thiobarbituric acid reactive substances (TBARS)] (50), enzymatic antioxidants [erythrocyte activity of the enzymes superoxide dismutase (SOD) and catalase] (20, 38, 41), and nonenzymatic antioxidants (total antioxidant capacity of plasma) (3) according to previously published methods. TBARS concentration was expressed in nanomoles MDA per milligram protein, SOD activity was expressed in units (U) per milligram of protein, and catalase activity was expressed by ΔE per minute per milligram protein, where ΔE represents the variation in enzyme activity for 1 min. The total antioxidant capacity was expressed as micrograms $FeSO_4$ per milligram of protein.

Physical and quality of life outcome measures. The assessments (exercise capacity, functional performance in ADLs, peripheral muscle strength, and quality of life) were performed in the same day and in the day after the blood collection.

The 6MWT was performed according to the guidelines of the ERS/ATS (28), and the best out of two tests was used for analysis. The predicted walking distance was calculated (17) and the peak oxygen uptake ($\dot{V}O_2$) during the test was estimated from 6MWD by prediction equation published previously (58). The functional performance in ADLs was assessment by five-repetition sit-to-stand test (5STS) (27) and timed up and go test (TUG) (49). During the 5STS the patients were asked to stand up and sit down, as fast as possible, five times with their arms crossed in front of their chest. Floor to seat height was 45 cm. The TUG was performed by timing the ability to stand up from a chair, walk 3 m, turn around, walk back to the chair, and sit down. Both 5STS and TUG were performed twice, with 2 min of recovery between the trials. The best of two trials was used for analysis.

The peripheral muscle strength was evaluated using a hand dynamometer (SH5001, Saehan, Korea). Peak handgrip strength (kgf) was measured at the dominant side, with the elbow in a 90° flexion and the forearm and wrist in neutral position. Three trials were performed and the highest value was taken for analysis. The handgrip strength-predicted values were calculated by reference equation (42).

Quality of life was evaluated through Saint George's Respiratory Questionnaire (SGRQ). The SGRQ examines the factors that respiratory disease inflicts on patients, such as symptoms, activity, and psychosocial impacts. Each domain has a maximum possible score; the points of each response are added together, and the total is referred to as a percentage of the maximum. Values >10% show that the quality of life has been altered in that domain. Reductions ≥4% after an intervention in any domain or the sum total of points indicate a clinically significant change in the quality of life of the subjects (29, 30).

Statistical analysis. The data were analyzed using the Statistica statistical package, version 10.0 and Graph-Pad Prism, version 5.0. The data are reported as means ± SD or as means (95% CI) unless stated otherwise. The Shapiro-Wilk and Levene test were applied to evaluate the normality and homogeneity of the results, respectively. At baseline, the Student's unpaired *t*-test (parametric data) or Mann-Whitney (nonparametric data) were used to compare measurements in the IG vs. CG. The effects of training were evaluated by ANOVA two-way design mixed test, which compare the principal effects in relation to the time and the interaction between the time (before and after) and groups (control × intervention). The paired *t*-test was used for post hoc comparisons. Effect size was described as partial eta-squared (Partial η^2). The calculation of sample size was based on 6MWD of the Pleguezuelos et al. (48) study. An alpha error of 0.05 and a power of 0.8 was selected, and reached a sample size of 8 subjects per group. The level of statistical significance was set up at $P < 0.05$.

RESULTS

In total, 66 patients were screened for eligibility. Of these, 32 did not meet the inclusion criteria and 7 refused to participate. Twenty-five COPD patients were included in this trial. Because 5 dropped out of the study (for reasons, see Fig. 1), 20 patients (10 in each group) completed the study and were considered for the final analysis (Fig. 1). At baseline, there were no significant differences in patient characteristics between the groups. The demographic, an-

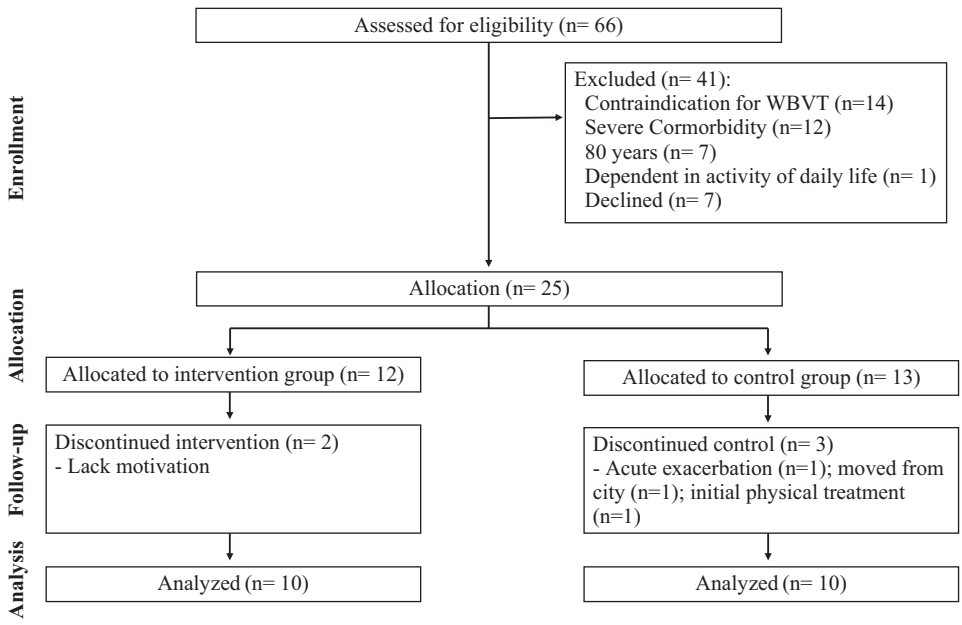

Fig. 1. Flow chart of the study. WBVT, whole body vibration training.

Table 1. *Demographic, anthropometric, and clinical characteristics at baseline*

Characteristics	CG (n = 10)	IG (n = 10)	P Value
Age, yr	63.5 ± 7.8	63.8 ± 8.1	0.9334
Sex, M/F	6/4	6/4	
BMI, kg/m^2	23.1 ± 4.5	23.3 ± 3.6	0.405[a]
FFMI, kg/m^2	16.7 ± 2.6	16.5 ± 2.7	0.828
Fat percentage, %	27.8 ± 8.2	28.5 ± 8.3	0.846
Lean mass, kg	39.7 ± 8.4	39.1 ± 9.4	0.896
Fat mass, kg	15.7 ± 7.1	15.5 ± 4.5	0.936
BMD, g/cm^2	1.0 ± 0.2	1.0 ± 0.2	0.743
FEV_1, % pred	58.2 ± 17.2	58.4 ± 21.4	0.982
FVC, % pred	74.9 ± 18.9	71.4 ± 21.1	0.701
FEV_1/FVC	56.1 ± 9.4	58.5 ± 9.6	0.315[a]
Smoker/former/non	4/4/2	4/4/2	
Pack-yr, n	34.3 ± 5.6	48.6 ± 5.2	0.079[a]
mMRC, points	1.2 ± 0.9	0.7 ± 0.9	0.231[a]
BODE index, points	2.3 ± 1.8	1.7 ± 1.4	0.612[a]
Inhalation medication, μg/day			
Bronchodilator	159.0 ± 114.8	244.2 ± 382.7	0.783[a]
Corticosteroid	607.1 ± 283.5	575.0 ± 373.8	0.763[a]

Values are means ± SD or number. BMI, body mass index; FFMI, fat-free mass index; BMD, bone mineral density; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; mMRC, modified Medical Research Council. P value: unpaired t-test or [a]Mann-Whitney test.

thropometric, and clinical variables are shown in Table 1. The inflammatory, oxidative, physical, and quality of life variables are shown in Table 2.

Patients from CG and IG showed normal body composition (BMI: 23.1 ± 4.5 and 23.3 ± 3.6 kg/m^2, respectively), moderate airflow obstruction (FEV_1: 58.2 and 58.4%, respectively), low dyspnea (mMRC: 1.2 and 0.7, respectively), and low impact of disease (BODE: 2.3 and 1.7, respectively). Moreover, the patients had an impaired exercise capacity (6MWD: 72.4 and 70.8% of predicted) and had preserved peripheral muscle strength (handgrip strength: 96 and 98.8% of predicted). In addition, at baseline, the global and differential white cell counts also were no significant different between groups ($P > 0.05$; data not shown).

The Tables 3 and 4 present the effects of WBVT regarding to the interaction between the time and groups. No statistical significance was found for inflammatory-oxidative biomarkers (Table 3) and white cell count (data not shown) in IG. Patients from IG showed a significant increase in exercise capacity, as demonstrated by increased 6MWD and $\dot{V}O_{2peak}$ compared with baseline and with CG (Table 4). Furthermore, the WBVT improved handgrip strength in IG compared with baseline and with CG. No statistical significance differences were found for 5STS and TUG in IG (Table 4).

Regarding the SGRQ, it was noted that all areas (total, symptoms, activity, and impact) did not show statistical changes at the end of the study. However, patients from IG showed a reduction (≥4%) in total and all domain scores, demonstrating clinically significant improvement. CG did not show significant improvement in all assessments, except for the reduction (>4%) in symptom domain of the SGRQ. The compliance at the training was of the 92.2 ± 10.9%. The demographic, anthropometric, and clinical variables did not change over the 12 wk in both groups (data not shown), and no adverse effects were reported.

DISCUSSION

To the best of our knowledge, this is the first study investigating the effects of WBVT on inflammatory and oxidative biomarkers in patients with stable COPD. The major finding of this study was that the WBVT enhances exercise capacity, muscle strength, and quality of life and does not alter inflammatory-oxidative biomarkers in patients with moderate COPD.

Table 2. *Inflammatory-oxidative, physical, and quality of life parameters at baseline*

Parameters	CG-*Week 0* (n = 10)	IG-*Week 0* (n = 10)	P Value
Inflammatory markers			
IL-8, pg/ml	26.9 ± 6.4	31.2 ± 12.9	0.248
IL-6, pg/ml	17.3 ± 3.1	15.4 ± 4.1	0.275
IFN-γ, pg/ml	0.94 ± 0.3	0.72 ± 0.2	0.06
sTNFR1, pg/ml	845.3 ± 213.6	1,036 ± 344.8	0.155
sTNFR2, pg/ml	1,883 ± 262.4	1,961 ± 604.9	0.714
Oxidative markers			
TBARS, MDA/mg protein	0.019 ± 0.01	0.023 ± 0.01	0.453§
Total antioxidant capacity, $FeSO_4 \cdot l^{-1} \cdot$mg protein^{-1}	2.66 ± 0.87	3.23 ± 0.82	0.153
SOD, U/mg protein	0.69 ± 0.42	0.91 ± 0.44	0.372
Catalase, $\Delta E \cdot min^{-1}$mg protein^{-1}	13.36 ± 5.83	15.67 ± 5.84	0.417
Physical tests			
6MWD, m	438.3 ± 126.9	423.9 ± 89.1	0.624§
6MWD, % pred	72.4 ± 19.8	70.8 ± 11.1	0.836
$\dot{V}O_{2peak}$, $ml \cdot kg^{-1} \cdot min^{-1}$	15.0 ± 2.9	14.9 ± 2.0	0.892
Handgrip, kgf	31.9 ± 7.4	34.1 ± 11.1	0.804
Handgrip, % pred	96.0 ± 11.5	98.8 ± 13.5	0.650
5STS, s	13.6 ± 4.7	11.5 ± 2.1	0.214
TUG, s	7.2 ± 1.9	6.4 ± 1.1	0.301
Quality of life			
SGRQ total, %	37.7 ± 16.9	39.1 ± 13.8	0.838
SGRQ symptoms, %	38.3 ± 19.6	34.3 ± 18.3	0.645
SGRQ activities, %	47.3 ± 18.8	50.3 ± 19.4	0.723
SGRQ impacts, %	32.1 ± 19.9	34.4 ± 14.5	0.766

Values are means ± SD. IL, interleukin; IFN, interferon; sTNFR, soluble tumor necrosis factor receptor; TBARS, thiobarbituric acid reactive substances; SOD, superoxide dismutase; 6MWD, 6-min walking distance; $\dot{V}O_{2peak}$, peak uptake oxygen; 5STS, five-repetition sit-to-stand test; TUG, timed up-and-go test; SGRQ, Saint George's Respiratory Questionnaire. P value: unpaired t-test or §Mann-Whitney test.

Table 3. *Treatment effects for inflammatory and oxidative markers*

Outcome	CG- *Week 12*	Δ (Change from Baseline)	IG - *Week 12*	Δ (Change from Baseline)	Interaction *P* Value	Partial η^2	Observed Power
Inflammatory markers							
IL-8, pg/ml	27.9 (21.2–34.6)	0.98 (−4.6 to 6.6)	31.5 (21.6–41.4)	0.4 (12.7 to 4.2)	0.89	0.001	0.05
IL-6, pg/ml	16.8 (14.2–19.4)	−0.5 (−1.7 to 0.7)	16.0 (13.3–18.7)	0.6 (−3.1 to 4.2)	0.53	0.022	0.09
IFN-γ, pg/ml	1.1 (0.8–1.4)	0.16 (−0.1 to 0.4)	0.9 (0.7–1.1)	0.2 (−0.1 to 0.4)	0.99	0.000	0.05
sTNFR1, pg/ml	868.4 (717.3–1,020)	23.1 (−103.5 to 149.7)	1,210 (970.7–1,148)	173.7 (−19.1 to 366.5)	0.23	0.080	0.22
sTNFR2, pg/ml	2,058 (1,825–2,291)	174.2 (28.3 to 376.7)	1,969 (1,498–2,439)	7.5 (−295.5 to 310.5)	0.41	0.038	0.12
Oxidative markers							
TBARS, MDA/mg protein	0.02 (0.02–0.03)	0.0 (0.0 to 0.01)	0.02 (0.02–0.02)	0.0 (0.0 to 0.01)	0.22	0.091	0.22
Total antioxidant capacity, $FeSO_4 \cdot l^{-1} \cdot mg\ protein^{-1}$	2.8 (2.3–3.2)	0.1 (−0.3 to 0.5)	3.0 (2.4–3.6)	−0.2 (−0.5 to 0.1)	0.25	0.072	0.20
SOD, U/mg protein,	0.9 (0.2–1.6)	0.2 (−0.5 to 0.9)	0.96 (0.1–1.8)	0.04 (−0.7 to 0.8)	0.74	0.001	0.06
Catalase, $\Delta E \cdot min^{-1} mg\ protein^{-1}$	13.3 (9.2–17.3)	−0,1 (−6.9 to 6.7)	15.3 (10.4–20.1)	0.4 (−6.8 to 6.0)	0.95	0.001	0.05

Values are means (95% CI). IL, interleukin; IFN, interferon; sTNFR, soluble receptor of TNF; TBARS, thiobarbituric acid reactive substances; SOD, superoxide dismutase. ANOVA 2-way design mixed (interaction analysis).

It is well known that exercise interventions trigger important adaptations in the immune system, depending on the type, duration, and intensity of the exercise (43, 46). The effect of exercise training on systemic inflammation in COPD is controversial. Some studies have shown that exercise training may impact on reducing inflammatory cytokines and oxidative stress (16, 47), whereas other studies failed (7, 72).

We strongly believe that the lack of difference in biomarker levels analyzed in the present study might be due to the organism adapting to training or a well-tolerated physiological stimuli by patients (14), because the WBVT protocol used in the present study was of low intensity (platform amplitude: 2 mm). In this context, previous studies demonstrated that in patients with heart failure (a chronic disease, which, like COPD, is characterized by a low-grade systemic inflammation), moderate-intensity exercise promotes better positive inflammatory-oxidative responses than low-intensity exercise (45, 53).

In line with our results, Cristi et al. (14) showed that 9 wk of WBVT in low intensity (platform amplitude: 2 mm) do not alter inflammatory markers (C-reactive protein, IL-6, IL-1β, IL-10, and TNF-α) in older adults. On the other hand, Rodriguez-Miguelez et al. (57) showed that 8 wk of WBVT in moderate intensity (platform amplitude: 4 mm) induced anti-inflammatory adaptations, by increasing IL-10 and decreasing pro-inflammatory markers, such as C-reactive protein and TNF-α, in elderly subjects. Thus our results are in agreement with previous studies showing that low-intensity modalities of exercise and low-intensity WBVT programs do not alter inflammatory-oxidative biomarkers in older adults and patients with chronic inflammatory disease.

Furthermore, our findings corroborate with other studies demonstrating that exercise training increases physical measures and quality of life without changing the inflammatory-oxidative response in stable COPD patients (7, 72). This is particularly important, since patients with COPD generally have increased levels of inflammatory-oxidative biomarkers in the circulation and, although the training did not produce positive inflammatory-oxidative responses, it also did not produce negative effects (69). Therefore, it is probable that the physical and quality of life changes occurred irrespective of the inflammatory-oxidative status and thus were dependent on other biological processes.

Our research showed an average increase of 65 m in the 6MWD, greater than 30 m (61) and 54 m (51) suggested previously as a minimum clinically important difference (MCID). This result is comparable to the increase of 55 m and 75 m in the Gloeckl et al. (23) and Braz-Junior et al. (8) studies, evaluating severe and very severe COPD patients, respectively. Moreover, the increased $\dot{V}O_{2peak}$ during 6MWT

Table 4. *Treatment effects for physical tests and quality of life*

Outcome	CG - Week 12	Δ (Change from Baseline)	IG - Week 12	Δ (Change from Baseline)	Interaction *P* Value	Partial η^2	Observed Power
Performance tests							
6MWD, m	439.2 (351.7–526.7)	3.6 (−16.3 to 23.6)	489.0 (424.9–553.1)	65.1(33.4 to 96.7)	**<0.001**	0.498	0.97
6MWD, % pred	72.7 (59.4–86.0)	0.3 (−2.7 to 3.3)	81.7 (72.3–91.1)	10.9 (5.2 to 16.2)	**0.002**	0.479	0.96
$\dot{V}O_{2peak}$, $ml \cdot kg^{-1} \cdot min^{-1}$	15.1 (13.0–17.1)	0.02 (−0.4 to 0.5)	16.2 (14.7–17.7)	1.4 (0.6 to 2.1)	**<0.001**	0.498	0.97
Handgrip, kgf	32.4 (26.7–38.2)	−0.9 (−2.9 to 1.1)	36.7 (25.7–47.8)	2.6 (0.01 to 5.2)	**0.02**	0.280	0.62
Handgrip, % pred	93.4 (85.5–101.3)	−2.7 (−8.8 to 3.4)	106.5 (92.3–120.7)	7.6 (0.7 to 14.5)	**0.01**	0.373	0.77
5STS, s	13.6 (11.3–15.9)	−0.4 (−2.2 to 1.5)	10.9 (9.2–12.7)	−0.5 (−2.2 to 1.2)	0.61	0.014	0.08
TUG, s	7.5 (6.3–8.7)	0.2 (−0.7 to 1.2)	6.5 (5.8–7.2)	0.1 (−0.5 to 0.6)	0.63	0.013	0.08
Quality of life							
SGRQ total, %	37.1 (26.5–47.7)	−0.6 (−5.0 to 3.8)	33.7 (20.5–46.9)	−5.4 (−15.6 to 4.8)	0.34	0.050	0.15
SGRQ symptoms, %	28.8 (15.3–42.2)	−9.5 (−22.4 to 3.3)	22.9 (12.83–33.0)	−11.4 (−25.6 to 2.8)	0.83	0.002	0.06
SGRQ activities, %	50.1 (38.8–61.3)	2.8 (−8.8 to 14.5)	46.2 (31.3–61.2)	−4.1 (−15.8 to 7.5)	0.35	0.048	0.15
SGRQ impacts, %	31.4 (17.9–44.7)	−0.7 (−6.8 to 5.4)	30.0 (15.8–44.2)	−4.4 (−15.4 to 6.6)	0.52	0.023	0.09

Values are means (95% CI). 6MWD, 6-min walking distance; 6MWT, 6-min walking test; $\dot{V}O_{2peak}$, peak oxygen uptake; 5STS, 5 repetition sit-to-stand; TUG, timed get up and go; SGRQ, Saint George's Respiratory Questionnaire. Bold values represent significant values. ANOVA 2-way design mixed (interaction analysis).

demonstrates that the energy demand during the vibration seems to be sufficient to raise the cardiorespiratory function in COPD patients. Indeed, previous studies showed that patients with COPD have increased $\dot{V}O_2$, respiratory rate (24), and heart rate (19) during vibration exercise. These responses seem to be the result of increased muscle activity (15), blood flow (33), and tissue oxygenation (56) of limbs during the vibration.

The 6MWT is a simple but very useful way to assess impaired exercise tolerance, which is an important clinical feature of COPD. The ERS/ATS has recommended that the 6MWT is an important outcome measure in the evaluation of pharmacological and nonpharmacological treatments for COPD (28, 61). Moreover, lower 6MWD is strongly associated with increased mortality risk and exacerbation-related hospitalization in COPD patients (64). Taken together, given the significant prognostic of the 6MWD and because walking is one the most frequent limitations in activities and participation of these patients (68), the 6MWD increase found in the present study may be associated with improvement in the exercise tolerance and mortality risk and hospitalization reductions.

In addition, the WBVT enhanced health status by improving quality of life in COPD patients. Our data showed that patients who received the training reached the MCID of 4 points for the SGRQ in the total and all domain scores. Similarly, Gloeckl et al. (21) and Braz-Junior et al. (8) showed that the MCID of the Chronic Respiratory Questionnaire (CRQ) and SGRQ, respectively, was reached by patients with COPD who performed the WBVT.

It is known that poor quality of life is one of the main determinants of the reduced 6MWD (66). Thereby we believed that the increased exercise capacity may have impacted on the quality of life. Although patients from CG reached the MCID in the symptoms domain of SGRQ, the low score was higher among IG patients. Because medication and dyspnea did not modify during the study, these variables may not influence the quality of life results in CG and IG. In this way, our data reinforce the WBVT effectiveness for improving exercise capacity and quality of life in COPD patients.

Complementary to these findings, the peripheral muscle strength increased in patients who performed the WBVT. Handgrip is a simple and feasible measure that can be used for assessing global muscle strength (6). In patients with COPD it was demonstrated that handgrip strength is strongly associated with the muscle strength of the upper and lower limbs (37, 70), particularly the quadriceps muscle (70). It is important to highlight that the present study is one of the few studies showing increased peripheral muscle strength in patients with COPD submitted to WBVT.

In accordance with our data, Spielmanns et al. (62) demonstrated that WBVT increased knee extensor strength in COPD patients. Nevertheless, the lack of the improvement in other studies may be related to different protocol studies. In fact, Gloeckl et al. (23) and Pleguezuelos et al. (48) offered the WBVT for 3 and 6 wk, respectively. In addition, the magnitude of energy transmitted (acceleration) to the body in the Salhi et al. (60) study was lower than that of the present study. Thus the discordance in the results could be due to time and intensity of the WBVT. The mechanism of vibration stimulus for increasing muscle strength is related mainly to increased neural muscle activation, mediated by tonic vibration reflex (10). Moreover, it is important to consider that beyond the tonic vibration reflex, the vibration stimulus seems to activate cortical motor areas and increase the excitatory state of peripheral structures involved with the movement (10, 39).

Interestingly, the ADL performance was not modified by WBVT. One probable reason for this could be due to good functional performance presented by patients in our study. The average times on 5STS and TUG tests were within the range of the normative values for healthy elderly subjects (5, 67). This good functional performance was probably related to satisfactory peripheral muscle strength and lower dyspnea (mMRC $<$ 2). In agreement with our results, previous studies have demonstrated association between peripheral muscle strength and the performance on 5STS (31) and TUG tests (54). Furthermore, the GOLD guidelines suggested mMRC $\geq$ 2 as a threshold for separating "less breathlessness" from "more breathlessness" (21a), where patients with scores $<$ 2 points have apparently few functional performance limitations (32).

In line with our results, Spielmanns et al. (63) did not show changes on the 5STS test in moderate COPD patients submitted to WBVT who had less impaired functional performance. Instead, Furness et al. (18) demonstrated significant improvement on 5STS and TUG tests in patients with moderate COPD who had times in these tests higher than the patients of the present study. Thus it is plausible to suppose that the WBVT in low intensity seems to be insufficient to increase ADL performance in patients with preserved functional performance.

Our study has some limitations. The first is the absence of randomization. Despite this, the allocation of patients between groups was performed in a paired manner. In addition, the researchers that assessed the participants were not aware of the allocation of the patients into the groups, which maintains the comparability of groups during the clinical trial and ensures an unbiased outcome assessment. Moreover, we cannot rule out the fact of that patients holding the upper limb onto bars of the platform may have influenced the increased handgrip strength. However, it is emphasized that this is a posture frequently adopted by patients in the studies (8, 48, 62). Additionally, because the $\dot{V}O_{2peak}$ was not measured directly, the $\dot{V}O_2$ values might be over- or underestimated. However, the comparison between the groups and changes over the time were not affected by this limitation. Finally, although the number of participants has been based in sample size calculation, the low sample size may have influenced the absence of significant statistical difference for some variables.

In conclusion, this study showed that the WBVT was related to beneficial effects on physical measures and quality of life in patients with stable moderate COPD and did not change the inflammatory-oxidative biomarkers. Moreover, the WBVT showed to be an integrated method, capable of improving cardiorespiratory and muscle components related to exercise capacity, quality of life, and peripheral muscle strength in moderate COPD patients.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

C.D.C.N., A.C.R.L., A.L.T., and V.A.M. conceived and designed research; C.D.C.N., V.K.S.L., A.A.S., M.G.A.C., L.P.L., T.J.S., E.L.M.V., M.A.M., and V.A.M. performed experiments; C.D.C.N., A.C.R.L., and V.A.M. analyzed data; C.D.C.N., A.C.R.L., and V.A.M. interpreted results of experiments; C.D.C.N. prepared figures; C.D.C.N., H.R.L., M.A.M., and V.A.M. drafted manuscript; C.D.C.N., A.C.R.L., V.K.S.L., H.R.L., M.A.M., and V.A.M. edited and revised manuscript; C.D.C.N., A.C.R.L., V.K.S.L., A.A.S., M.G.A.C., L.P.L., T.J.S., E.L.M.V., A.L.T., H.R.L., M.A.M., and V.A.M. approved final version of manuscript.

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