Original article

DOI: 10.5114/areh.2022.123180

Advances in Rehabilitation, 2022, 36(4), 24–32

Stress Axis Response to Aerobic Exercise in Chronic Obstructive Pulmonary Disease Patients

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A – Research concept and design
B – Collection and/or assembly of data
C – Data analysis and interpretation
D – Writing the article
E – Critical revision of the article
F – Final approval of article

Received: 2022-09-10
Accepted: 2022-08-12
Published: 2022-12-16

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Abstract

Introduction: COVID mortality is particularly high among patients with comorbidities; this may be due to psychological stress caused by overactivation of the stress axis. The study investigates the effect of home-based physical activity (HBPA) on the stress axis in patients with chronic obstructive pulmonary disease (COPD).

Material and methods: Forty men aged 55–68 years with stable COPD were randomly divided into study or control groups. The study group (n = 20) received eight-week HBPA, three sessions per week, while the control group (n = 20) did not. The following measurements were taken for both groups: body mass index (BMI), pulmonary function test (PFT), cortisol, interleukin-8 (IL-8), health-related quality of life assessed as total St. George's Respiratory Questionnaire (SGRQ) score, hospital anxiety and depression scale score (HADS), and 6-minute walking test (6MWT).

Results: All variables of the control group showed non-significant improvement. Significant improvements in cortisol (262.15 ± 25.08 vs 219.80 ± 30.68 ng/mL; $p < 0.001$), IL-8 (15.00 ± 5.64 vs 12.26 ± 5.07 pg/ml; $p < 0.001$), HADS (7.85 ± 2.56 vs 5.36 ± 2.68 and 8.75 ± 2.46 vs 6.60 ± 2.70; $p < 0.001$ for depression and anxiety subscales, respectively), SGRQ total score (40.50 ± 11.70 vs 35.90 ± 11.75; $p < 0.001$), and 6MWT (514.85 ± 22.49 vs 575.90 ± 34.37; $p < 0.001$) were found in the study group over time. No change was observed for BMI and PFT.

Conclusions: HBPA is a good tool for improving cortisol, IL-8, HADS, SGRQ, and 6MWT level in COPD patients, especially during the COVID pandemic.

Keywords: COPD, COVID-19 pandemic, exercise, stress, hypothalamic-pituitary-adrenal

Introduction

Subjects with chronic comorbidities such as chronic obstructive pulmonary disease (COPD) demonstrated a particularly high death rate during the coronavirus disease-2019 (COVID-19) pandemic. Such a state of affairs can elevate the risk of mental/physical health issues. Some of these health issues, such as stress and depression, were found to persist in patients who had completed quarantine. In particular, older patients demonstrate less resilience in the hypothalamic-pituitary-adrenal (HPA) or stress axis and lower adaptive recovery from repeated stress, which negatively impacts COPD progression [1].

Repeated exposure to chronic stress weakens the regulating mechanisms of the HPA axis and increases its main end-product, cortisol. Moreover, in patients with long-term chronic diseases, including COPD, HPA activity produces elevated basal levels of cortisol and chronic systemic inflammatory mediators (*e.g* interleukin-8, IL-8), even in non-stressful conditions. Besides low functional outcomes such as low quality of life (QoL) and exercise intolerance, hypercortisolemia increases the risk of depression, anxiety, cardiovascular disease, sleep/appetite changes, hypertension, reduced immunity, increased hospitalization, and mortality risk in COPD patients [2].

Exercise is regarded as the cornerstone complementary treatment in the management of COPD and its comorbidities. Exercise can improve functional capacity, anxiety and depression, rate of exacerbations, stress, fatigue, systemic inflammation, dyspnea, and rate of hospitalization in patients with COPD [3]. Moreover, exercise can increase the ability of patients to cope with longstanding COPD [4].

During the repeated social isolation times of the COVID-19 pandemic, there were repeated calls to increase home-based physical activity (PA) in COPD patients. However, while regular exercise was documented to improve the risk of respiratory tract infection, physical and psychological conditions, disturbances of the HPA axis, systemic inflammation, health-related QoL, and exercise capacity in COPD patients, the level of adherence by COPD patients to face-to-face medical/rehabilitation services was found to fall [1].

Many patients with chronic disorders, including COPD, may be more vigilant when attending face-to-face medical assessment or rehabilitation in governmental or private health settings due to the increased understanding of COVID-19 cross-infection. This attitude may worsen attendance at supervised PA programs in settings such as health gyms and physiotherapy centers. Hence, the aim of the present was to determine whether home-based PA had any effect on the stress axis in men with COPD during the COVID-19 pandemic.

Materials and methods

Participants

All procedures of this study were conducted according to the International Declaration Tents of Helsinki. The study protocol was approved by the Research Ethical Committee (Faculty of Physical Therapy/Cairo University) (approval number P.T.REC/012/002897).

In total, 40 men aged 55 to 68 years with stable COPD, i.e. free from exacerbation for more than three months, were recruited from Mit Ghamr, Dammas, and Mit Yaish Central Hospitals. All participants were patients with COPD who had been attending regular follow-ups at the chest-disease outpatient clinics before the COVID-19 pandemic. The patients were then contacted by phone to present the study and ask for their consent to take part.

The participants were non-smokers at study entry, had not participated in any physical activity program in the previous six months, and had a cycle or treadmill at home. The exclusion criteria were the presence of systemic/cardiovascular disorders, previous COVID-19 attacks, neuromuscular problems, and hepato-renal diseases. Patients were also excluded if they were on supplemental oxygen therapy or had another chest disease, autoimmune disease, connective tissue disorders, cancer or psychiatric disease. All participants were randomly divided into a study group (n = 20), which received an eight-week home-based PA program three times per week, or a control group (n = 20), which did not. They were assigned using sequenced random closed-envelope allocation by an independent physiotherapy assistant. Figure 1 depicts the flow chart for this research trial.

Outcome measures

Body mass index (BMI), was tested, together with FVC and FEV1 as pulmonary function tests (PFT), the day before the start of PA and the day after it ended. Plasma levels of cortisol were measured in the morning, at 8:00 am, and IL-8 was estimated by ELISA. In addition, the 6-minute walking test (6MWT) score was taken, in meters, to assess functional capacity before and after training.

The participants completed the hospital anxiety and depression scale (HADS). The 14-item HADS tool comprises anxiety and depression subscales. Each item of HADS is scored on a four-point scale, giving the maximum anxiety and depression scores of 21 per item. On either subscale, scores ≥11 are considered to indicate significant psychological morbidity, 8–10 as borderline and 0–7 a normal state.

The St. George's respiratory questionnaire (SGRQ) was used to determine the quality of life related to chest diseases including COPD.

A 5ml venous blood sample was taken from all participants by a nurse before and after the PA program for testing cortisol and IL-8 levels. In addition, SGRQ, BMI, 6MWT, and HADS was evaluated by a physiotherapy assistant with five years of physiotherapy experience; the assistant did not participate in the PA program. FVC and FEV1 were also measured before and after the study using a portable spirometry device, by a spirometry technician with five years of experience. Neither the laboratory specialist, physiotherapy assistant or spirometry technician were informed of the cause of the analysis and the nature of the applied PA interventions.

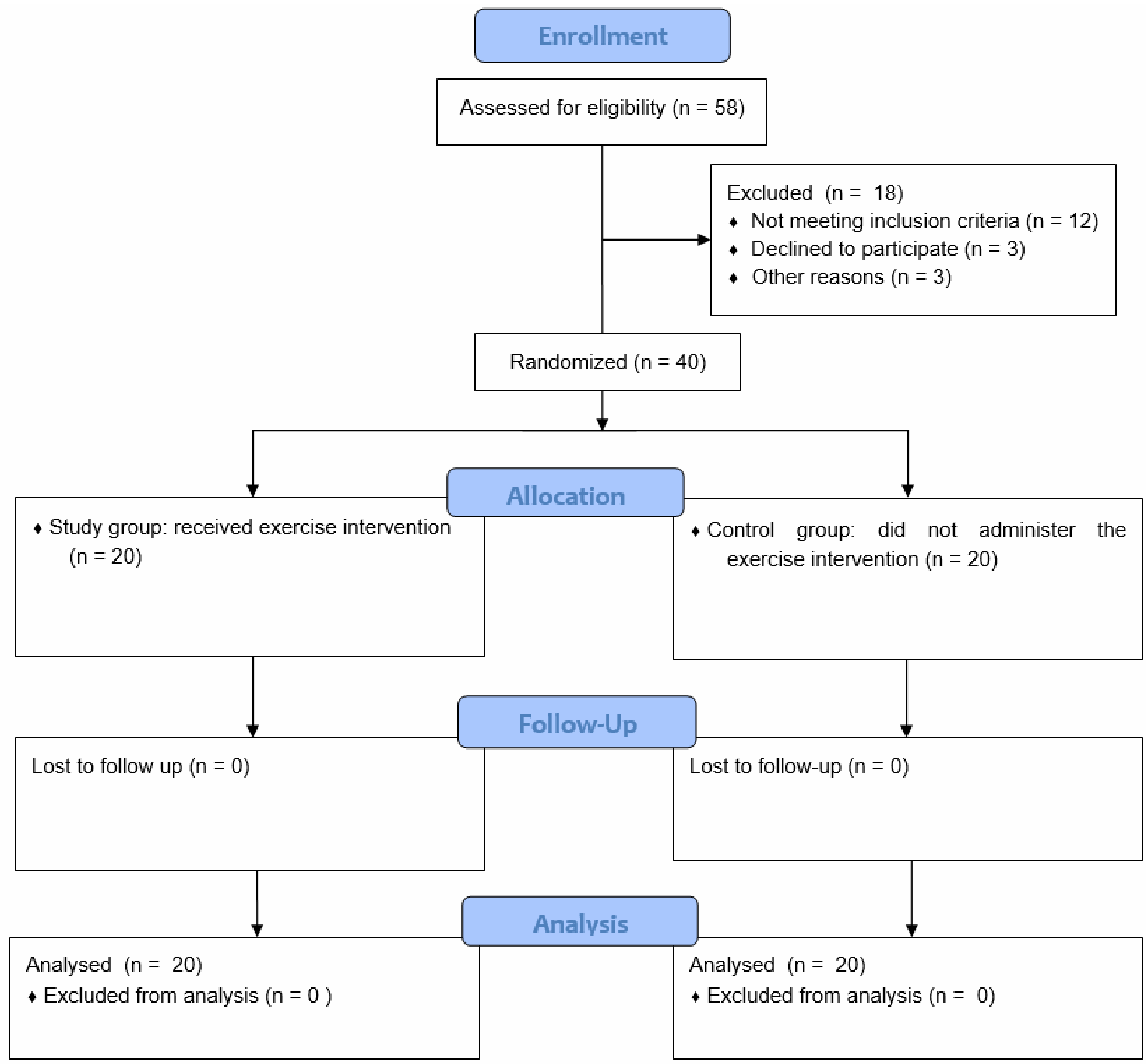

Fig. 1. Consort flow diagram of the study

Interventions

This study was completed during the period from 19th November 2020 to 1st March 2021. The participants in the intervention group received three sessions of home-based PA (HBPA) program three times a week. Each session was composed of 50-minute cycling or treadmill walking, followed by 30-minute upper/lower limb exercises, followed by a 30-minute educational training session.

On the same day that the outcome measurements were taken, each participant received a face-to-face interview in which the contents of the program were explained: cycling or treadmill walking, upper and lower limb exercises, and educational training stages. The first session was supervised in a private rehabilitation center. From the second session, the exercise program was conducted at home.

The main phase of continuous ergometric cycling or treadmill walking was conducted with moderate intensity at 60–70% of maximal heart rate (HRpeak), calculated as (220 – age in years), for 40 minutes. The main phase was preceded with a 5-minute warm-up and followed by a 5-minute cooldown at 40% HRpeak.

After finishing the cycling or treadmill walking, patients were allowed to rest for two hours. Then, the patients performed 30-minute active free upper and lower limb exercises without resistance. For the upper limbs, the sequence of the exercise was bilateral shoulder abduction, flexion, and diagonal exercises (2.5 minutes for each direction). For lower limbs, the sequence of exercises was unilateral abduction, unilateral knee-to-chest flexion, unilateral straight leg raising, standing calf raises, and unilateral knee-to-chest exercises while standing (2.5 minutes for each direction). Each patient was supplied with a wristband heart-rate monitor to help them maintain 60–70% HRpeak during the home-based exercise session on the cycle or treadmill or during limb exercises.

After finishing the limb exercises, patients were allowed to rest for two hours. Then, the patients performed a 30-minute educational training session (7.5-minute relaxation, 7.5-minute chest clearance techniques, 7.5-minute diaphragmatic exercise, and 7.5-minute pursed-lip breathing).

The author monitored the performance of all parts of the home-based PA program online. During each HBPA session, and during the study period, a family member assisted the researcher in supervising the patient using a mobile phone with the IMO video-call Android application.

Statistical analysis

The Kolmogorov-Smirnov test confirmed that the obtained data demonstrated a normal distribution. The between-group differences in demographic data (weight, age, BMI, and Height), clinical data (blood pressure, FEV1% predicted, saturated O_2, and FEV1/FVC), and outcomes (FVC, FEV1, cortisol, IL-8, HADS depression and anxiety, SGRQ total score, and 6MWT) were analyzed with the unpaired T-test. The within-group differences in the same outcomes, as well as BMI, were examined with the paired T test, assuming a significance of p value < 0.05.

Results

No statistically significant difference was found between the study and control groups regarding pre-treatment demographic or clinical data (Tab. 1), or pre-treatment outcomes (Tab. 2) via the unpaired T-test ($p > 0.05$).

The study group demonstrated significant differences over time in cortisol, IL-8, 6MWT, SGRQ total score, and HADS (depression and anxiety) score, while no significant different differences were found for BMI and pulmonary functions (FVC and FEV1) (t-test; $p > 0.05$). No such changes in any variables were observed in the control group (Tab. 2).

At the end of the study, significant differences in cortisol, IL-8, 6MWT, SGRQ total score, and HADS (depression and anxiety) were found between groups in favor of the study group ($p < 0.05$). However, no such differences were found for BMI or pulmonary functions (FVC and FEV1) ($p > 0.05$) (Tab. 2).

Discussion

Efforts should be made to manage the stress levels experienced by COPD patients during the COVID-19 pandemic to maintain low levels of systemic inflammatory markers and cortisol through maintaining the finely-balanced functions of the HPA axis. Our present

Tab. 1. Demographic and clinical data of groups

Group data		Study group Mean ± SD	Control group Mean ± SD	p-value
Age [year]		60.35 ± 4.35	59.35 ± 3.82	0.444
Weight [kg]		77.54 ± 12.6	78.87 ± 13.8	0.752
Height [cm]		168.27 ± 7.8	169.34 ± 7.5	0.660
BMI [kg/m^2]		26.35 ± 1.92	26.30 ± 1.75	0.932
FEV1 [% predicted]		64.10 ± 9.71	63 ± 10	0.726
FEV1/FVC [%]		63.07 ± 7.65	62 ± 6.95	0.646
Heart rate [beat/min]		74.5 ± 12.9	75.3 ± 13	0.846
Saturated O_2 [%]		94 ± 2.2	95 ± 1.9	0.132
Systolic blood pressure [mmHg]		125 ± 16.4	124.64 ± 15.32	0.943
Diastolic blood pressure [mmHg]		79 ± 9.2	78 ± 8	0.715
Gold stage	Stage I	n = 3	n = 4	
	Stage II	n =17	n =16	

BMI − body mass index, FEV1 − forced-expiratory volume in one second, FVC − forced vital capacity, kg − kilogram, n − number, O_2 – oxygen, p − probability, significant difference (p-value < 0.05).

Tab. 2. Between-group and within-group data analysis

Group data	Study group	Control group	p- value (among-groups)
BMI [kg/m^2]	Mean ± SD	Mean ± SD	
Pre	26.35 ± 1.92	26.30 ± 1.75	0.932
Post	26.06 ± 2.09	26.46 ± 1.61	0.497
p-value (within-group)	0.180	0.442	
FVC [L]	Mean ± SD	Mean ± SD	
Pre	1.93 ± 0.53	1.92 ± 0.52	0.948
Post	2.10 ± 0.75	1.84 ± 0.537	0.224
p-value (within-group)	0.05	0.237	
FEV1 [L]	Mean ± SD	Mean ± SD	
Pre	1.08 ± 0.189	1.07 ± 0.173	0.911
Post	1.16 ± 0.265	1.03 ± 0.222	0.099
p-value (within-group)	0.07	0.056	
Cortisol [ng/mL]	Mean ± SD	Mean ± SD	
Pre	262.15 ± 25.08	262.40 ± 24.08	0.975
Post	219.80 ± 30.68	262.85 ± 23.43	< 0.001*
p-value (within-group)	< 0.001*	0.911	
IL-8 [pg/ml]	Mean ± SD	Mean ± SD	
Pre	15.00 ± 5.64	14.84 ± 6.08	0.932
Post	12.26 ± 5.07	15.75 ± 5.75	0.049*
p-value (within-group)	< 0.001*	0.178	
HADS depression	Mean ± SD	Mean ± SD	
Pre	7.85 ± 2.56	7.35 ± 2.58	0.542
Post	5.36 ± 2.68	7.45 ± 2.43	0.014*
p-value (within-group)	< 0.001*	0.799	
HADS anxiety	Mean ± SD	Mean ± SD	
Pre	8.75 ± 2.46	8.45 ± 2.32	0.695
Post	6.60 ± 2.70	8.60 ± 2.50	0.020*
p-value (within-group)	< 0.001*	0.448	
SGRQ total score	Mean ± SD	Mean ± SD	
Pre	40.50 ± 11.70	45.40 ± 12.58	0.210
Post	35.90 ± 11.75	46.10 ± 12.63	0.012*
p-value (within-group)	< 0.001*	0.273	
6MWT [m]	Mean ± SD	Mean ± SD	
Pre	514.85 ± 22.49	513.90 ± 22.06	0.893
Post	575.90 ± 34.37	513.30 ± 21.09	< 0.001*
p-value (within-group)	< 0.001*	0.906	

BMI – body mass index, HADS – hospital anxiety and depression scale, IL-8 – interleukin-8, FEV1 – forced-expiratory volume in one second, FVC – forced vital capacity, kg – kilogram, n – number, O_2 – oxygen p – probability, significant difference (*p-value < 0.05), SGRQ – St. George's respiratory questionnaire, SD – standard deviation, 6MWT – 6 minute walk test.

findings indicate that eight-week home-based physical activity (HBPA) lowered cortisol levels, anxiety, and depression in COPD patients.

The prolonged exercise training, in the form of treadmill walking or bicycling, used in this study resulted in improved depression and anxiety. Long and regular exercise improves the symptoms of depression and anxiety by increasing the stability of the HPA axis and endogenous opioid production. A stable HPA axis can lower cortisol levels and reduce COPD-associated systemic inflammation. Reduced systemic inflammation may reduce the commonly reported levels of depression and anxiety in chronic diseases [5].

The improvement in the perception of COPD symptoms following exercise may explain the improvement in the St. George's Respiratory Questionnaire (SGRGQ). Exercise training has been associated with a distraction from annoying thoughts, increased pleasant sensations during daily events or activities, and decreased feelings of anger, tension and irritability. This may improve the patient's perception and bearing regarding COPD symptoms and improve the quality of life of COPD sufferers [6].

Improved cortisol and functional capacity (6MWT) were noted over the eight-week training period. In addition, plasma cortisol production may have been inhibited by deactivation of the HPA axis, resulting in lower levels; in older men, chronic training has been associated with beneficial effects such as increased anabolism and reduced response to catabolic hormones. Fortunately, the decreased levels of cortisol, a catabolic hormone, may extend to exercise-free periods, which are also associated with increased production of adapted neurotransmitters known to increase muscle mass (hypertrophy), reduce muscle loss, and improve muscular strength and functional capacity; they also regulate the metabolism of glucose and insulin in the elderly. Cortisol response and adaptation to exercise may be influenced by gender, age and training status, as well as by training parameters such as frequency, volume, duration, intensity and type. As such, these require further studies [7,8].

In contrast to our present findings, cortisol levels in seniors aged 60–90 years were not found to decrease after 10-week aerobic walking; however, this may be due to the study using a different method of cortisol assessment [9]. Even so, an early study on nine seniors (mean 62 ± 3.2 years) showed a significant decrease of plasma cortisol after 10-week resistive training associated with changes in exercise intensity (resistance workouts) and volume (repetitions sets) per week [10].

While Izquierdo et al. also report a significant decrease in cortisol in seniors after four-month progressive resistive training, the same authors also indicate a non-significant cortisol improvement in middle-aged trained participants [11]. Interestingly, another study found a six-month resistance-training protocol produced non-significant improvement in cortisol in middle-aged or elderly participants [12].

In contrast to the significant improvement of plasma cortisol noted in the present study, Baker et al. [13] found women to show a significant decrease in cortisol level after aerobic exercise; however, this may be due to women demonstrating higher resting cortisol levels than men. One study found a significant decrease in cortisol in 12 women aged 54.83±2.79 years (mean BMI 26.87 ± 2.15 kg/m^2) after eight-week treadmill running [9], while another noted no significant changes after 12-week water-based aerobic exercise in 13 elderly women aged 68.89 ± 4.70 years [14].

The addition of a 10-week exercise training to a stress management program in COPD patients produced more favorable responses in endurance, cognitive performance, and anxiety [15]. However, an eight-week PA programme was selected for the present study based on a number of previous studies [16,17]. Mkacher et al. [17] report significant changes in cortisol and 6MWT, and insignificant changes in PFT and BMI, after eight-week PR in men with COPD. Also eight-week PA was found to significantly improve SGRQ and 6MWT in seniors with COPD [18]. In addition, Wadell et al. [19] report significantly improved HADS and total SGRQ in COPD patients receiving an eight-week PA program, but no such improvement in the control group receiving usual care.

Similar to our present findings, Tsai et al. showed that eight-week real-time videoconferencing PA was able to improve QoL, 6MWT, and HADS in elderly with COPD while improvement was noted in a control group receiving only medication [20]. It was also found that 14-week PA produced non-significant improvements PFT and significant improvements in QoL (assessed by SGRQ) and 6MWT [21,22]. In addition, another study demonstrated a significant improvement in SGRQ score in 14 COPD patients after eight weeks of aerobic training (2 sessions/week) at 40-60% of HR-peak [23].

It was also found that 23 sessions of 90-minute exercise significantly lowered IL-8 levels and total SGRQ score in elderly patients with COPD, which was attributed to the anti-inflammatory epigenetic machinery properties of exercise [24]. When added to traditional physical therapy for COPD, exercise was found to positively affect the levels of sputum IL-8 [25]; it was also found that the significant decrease in IL-8 levels observed after two months of HBPA continued to a six

– month follow-up [26]. Eight weeks of aerobic training in elderly COPD patients was also found to significantly lower IL-8 levels [27].

However, in contrast to our present findings, eight-week outpatient PA produced non-significant changes in systemic inflammatory markers in COPD elderly patients despite significant changes in SGRQ and HADS [28]. In addition, another study found eight-week HBPA to result in non-significant changes in IL-8 in seniors with COPD, despite yielding a significant improvement in walking distance [29]. Vanfleteren et al. report no significant changes in IL-8 levels after 40 PA sessions in overweight seniors with COPD, but obtained similar results to ours regarding BMI, PFT, SGRQ and 6MWT [30]. In addition, Marques et al. report insignificant changes in total SGRQ score after 12-week PR (mean change = − 4.3 units, p = 0.089); however, exercise significantly improved 6MWT [31].

Eight-week PA was not found to improve HADS in preobese COPD elderly; however, as in the present study, insignificant improvements were noted in lung function (except FEV1%, p=0.005) and BMI, and significant improvements in 6MWT and total SGRQ score [32]. Elsewhere, similar lung function results were achieved by eight-week endurance and resistance training (two sessions weekly) in seniors with COPD, but no significant changes in SGRQ and HADS scores were found [16]. In addition, a video-based home training program failed to improve HADS in a COPD group, while an insignificant improvement in HADS was noted in the non-exercised control group, as noted in the present study [33].

It is correct to assume that the treatment program employed in the present study is similar to pulmonary rehabilitation programs given in previous studies. However, the present study describes its use during periods of social distancing in the COVID epidemic, imposed either by law or by some COPD patients themselves. Our findings therefore represent a distinct addition in treatment, as it is intended not only to improve the quality of life, functional ability, stress, depression, and anxiety associated with isolation, but also to reduce the negative impact of the high levels of cortisol hormone and this on the markers of chronic systemic inflammation.

Clinically speaking, HBPA is a good exercise modality for maintaining the health status of patients during lockdown or social distancing. This is particularly true for COPD patients who are unable to attend rehabilitation services, especially during the COVID pandemic.

The main limitation of this study is its relatively short follow-up period. Therefore, future COPD research should employ longer follow-up periods to confirm whether the improvements in HADS, SGRQ, cortisol, 6MWT, and IL-8 are sustained. In addition, the study observes the response of HADS, SGRQ, cortisol, 6MWT, and IL-8 to different exercise protocols, including resistance training and different age classes, which may be a source of heterogeneity.

Conclusions

During periods of lockdown, social distancing, and repeated pandemic waves, HBPA (home based physical activity) is a good tool for improving functional capacity, quality of life, systemic inflammation, stress, depression and anxiety in COPD patients, and for decreasing the need for repeated visits to physical therapy centers.

Funding
This research received no external funding.

Conflicts of Interest
The authors have no conflict of interest to declare.

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