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ORIGINAL ARTICLE

LENGTH OF EXERCISE TRAINING IN COPD: A SINGLE-SUBJECT DESIGN

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Keywords: Chronic Obstructive Pulmonary Disease COPD), exercise training, single-subject design.

Background: The minimum duration of exercise training in patients with Chronic Obstructive Pulmonary Disease (COPD) is still discussed.

Objectives: To study, over time, the effects of a lower-limb endurance-training program in a patient with COPD, evaluating when changes in the exercise capacity initiate and if these changes stop occur during the intervention period.

Methods: A 73-year-old male with severe COPD (FEV_1: 0.92 L, 37.5 % predicted) performed three 30-minute training sessions per week, during 12 weeks, at 70% of peak work rate. A metabolic analyzer system was used at regular intervals, during an incremental, symptom-limited cycle ergometer exercise test. Peak and isowork exercise variables were studied. Data were analyzed with visual analysis, associated with Kappa statistic, two-standard deviation band, celebration line and regression analysis ($p < 0.05$).

Results: The following changes were observed with exercise training: peak exercise variables as work rate, carbon dioxide output, and ventilation ($\dot{V}E$) significantly increased at a same workload; oxygen uptake ($\dot{V}O_2$), $\dot{V}E$, perceived exertion and heart rate decreased and peripheral oxygen saturation (SpO_2) increased significantly. Changes in exercise capacity verified by $\dot{V}E$, $\dot{V}O_2$, perceived exertion and SpO_2, at isowork condition, were observed in the fourth week of training. Regression analysis showed that $\dot{V}O_2$ and respiratory frequency decreased significantly in the course of intervention, while tidal volume and SpO_2 increased during this phase.

Conclusions: The patient improved his exercise tolerance after the training program. Changes in exercise capacity initiated in the fourth week of intervention and continued until the end of the training.

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INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a preventable and treatable disease characterized by chronic airway limitation that is not fully reversible[1]. Reduced exercise tolerance is one of the most troubling manifestations of COPD and contributes to restrict activities of daily living in these patients[2,3]. The consequent inactivity leads to progressive deconditioning which, in turn, is aggravated by the systemic effects of the disease[4]. Due to the physiopathological heterogeneity of COPD and the various comorbidities associated with this disease, the mechanisms of exercise intolerance in patients with COPD are multifactorial, reflecting the integrated abnormalities of respiratory, cardiovascular, metabolic and neuromuscular systems. Accordingly, the exercise tolerance in patients with COPD is the result of a complex interaction between central factors (ventilation, dynamic hyperinflation and dyspnea) and peripheral factor (atrophy and muscle weakness and fatigue)[3, 5].

Endurance training in the form of cycling or walking exercise is the most commonly applied training modality in pulmonary rehabilitation[3]. Although it has been extensively demonstrated that lower-limb endurance exercise training improves exercise capacity, exertional dyspnea and heath-related quality of life (HRQL) in patients with COPD[6], the optimal length of exercise training programs remains a debated topic, and to date there is no consensus on how long they should last[3, 7-10].

Green *et al.*[7] compared the effects of a twice weekly outpatient program of disease education and exercise training including aerobic walking (intensity was not specified), general mobility and strength training performed during four or seven weeks. They showed those patients who underwent the 7-week program presented greater improvement in health-related quality of life outcomes, including the dyspnea domain of Chronic Respiratory Questionnaire (CRQ); however no statistically significant differences were found between groups on exercise capacity, Shuttle Walking Test (SWT) and treadmill endurance test. On the other hand, Sewell *et al.*[9], showed that a 4-week supervised program of twice-weekly sessions including education and exercise, strength and aerobic training at 85% of predicted peak VO_2 plus home sessions, was equivalent to a 7-week program. Overall, no statistical differences were found between groups on health-related quality of life (CRQ) and exercise capacity (SWT).

The recommendations about the minimum duration of rehabilitation programs differ considerably in guidelines, varying from four to twelve weeks[3,11]. Although measurable physiological changes may occur with shorter rehabilitation programs (4-8 weeks), longer programs may potentially render larger and more comprehensive benefits, mainly regarding patient's behavior changes. Furthermore, even though 12-week training programs are usually carried out in clinical trial[12,13], it is not clear if this period of training is enough to stabilize changes.

In this context, the aim of this study was to document, over time, the effects of a lower-limb endurance-training program in a patient with COPD, evaluating when changes in the exercise capacity initiate and if these changes stop occur during the intervention period.

METHODS

This study was approved by the Ethics Committee of the institution (0401/06) and followed the Resolution 196/96 of the National Health Council. After being informed of the nature of the project, the participant signed the informed consent term.

Design and subject

This study was a single-subject experimental design with two phases: baseline (phase A) and intervention (phase B). Phase A consisted of repeated assessments of participant exercise capacity by means of cardiopulmonary exercise testing without intervention. Phase B consisted of intervention and periodic assessments. Phase A and B lasted six and twelve weeks, respectively, totaling eighteen weeks of study. A 73-year-old patient with severe COPD, according to the Global strategy for the diagnosis, management, and prevention of Chronic Obstructive Pulmonary Disease[1] was recruited. The baseline spirometry were, forced expiratory volume in one second (FEV_1): 0.92L, 37.5% predicted; forced vital capacity (FVC): 2.48 L, 76% predicted; FEV_1/CVF: 0.37)[14]; and smoking habit of 50 packs/year for 40 years; body mass index of 22.4 kg/m^2.

Measurements

After collecting clinical data and measuring height and weight of the subject, Medical Research Council (MRC) scale and the Human Activity Profile (HAP)[15], were used to characterize subject's dyspnea and level of physical activity, respectively, at the beginning of the study.

Cardiopulmonary exercise testing

Cardiopulmonary exercise testing was used to evaluate the participant exercise capacity during baseline (phase A) and intervention (phase B) phases. During the baseline, weekly assessments were carried out during a six-week period. In the intervention phase, assessments were conducted every 15 days. In this way, 12 repeated measurements were undertaken in the end of the study, six during phase A and six during phase B. The number of assessments in baseline was based on the recommendation that to determine the stability of a response at least 5 points are necessary[16]. The assessments were done always in the morning by a blind evaluator who was not responsible for the intervention. During the exercise testing, a breath-by-breath automated metabolic analyzer system (Medical Graphics® CPX Ultima, Miami, FL, USA) was used to measure continually the airflow and, simultaneously, to determine expired carbon dioxide and oxygen concentrations, considering the recommendations for calibration procedure[17]. Additionally, a facemask was carefully adjusted to the patient's face and checked for air leaks in each assessment during phases A and B.

Incremental symptom-limited exercise tests were performed on a cycle ergometer (Ergo Cycle 167, Pirmasens, Germany) following the recommendations of American Thoracic Society (ATS) and the American College of Chest Physicians Statement, including the criteria for terminating exercise test[17]. During all the tests, a 12-lead electrocardiograph (Welch Allyn, Skaneateles Falls, NY, EUA) was used to monitor the patient[17]. Heart rate (HR) and peripheral oxygen saturation (SpO_2) were continuously measured with blood pressure every two minutes. The modified Borg scale was used to determine patient's perceived exertion. At the end of the test, participant was asked to inform the reason for exercise test cessation: dyspnea, fatigue and both or other reasons.

Intervention

The 12-weeks training program consisted of 1.5-hour training sessions, which the patient attended three times per week. In the beginning and end of each session, a Physical Therapist measured blood pressure, HR, *f* and did pulmonary auscultation. After a period of warm-up, the exercise on the cycle ergometer at the training work rate was performed, followed by a recovery period. During the warm-up and recovery period, the patient stretched out the lower-limb muscles and cycled at a work rate of 15 watts. The training on the cycloergometer was performed at 70%[12] of the average of peak work rates obtained during baseline phase, with pedaling frequency of 60 rpm, aiming to reach 30 minutes pedaling at this intensity. The duration of pedaling at the training intensity was defined by patient's tolerance or by the occurrence of some indication for exercise termination[17]. In this way, when it was necessary, the work rate of the cycle ergometer was reduced to its minimum and was returned when the patient was considered able to come back to the training intensity.

Variables

The following variables were analyzed during the baseline and intervention phase: work rate (WR), oxygen uptake ($\dot{V}O_2$), carbon dioxide output ($\dot{V}CO_2$) and minute ventilation ($\dot{V}E$) at peak work rate, and $\dot{V}O_2$, $\dot{V}E$, tidal volume (Vt), respiratory frequency (*f*), perceived exertion, HR and SpO_2 at a same workload (isowork exercise variables).

Data analyses

The peak work rate of each cardiopulmonary exercise testing was defined as the last work rate the participant was able to sustain for at least 20 seconds[18]. For comparing the variables at identical levels of exercise (isowork), it was selected the peak work rate of the shorter incremental test of the baseline phase[19]. After obtaining breath-by-breath data, they were averaged every 15 seconds[20]. To evaluate the quality of exercise testing results, two independent assessors with experience in the application of the procedures evaluated all exercise tests with respect to some aspects, including presence of fluctuations (noise) in the ventilatory and metabolic variables and initiation of ventilatory response with the increment in work rate.

Statistical analysis

Baseline and intervention responses were compared using Visual Analysis and two statistical methods: the Two Standard Deviation Band (TSDB) and the Celeration Line (CL). These three methods were selected based on the recommendation[21] that significance and direction of change in each study phase are accepted only if indicated by at least one statistical method (TSDB or CL) and corroborated by visual analysis[21].

Visual analysis was performed by three independent assessors blinded for the variable to be assessed. The aspects evaluated were change in tendency (stable, accelerating or decelerating) and magnitude (increase or decrease) of responses when comparing phase B to phase A. Changes in magnitude were considered only if data showed the same trend in both phases. Besides, the points where these change initiated in phase B were evaluated when data were accelerating or decelerating in this phase. The agreement between assessors was evaluated using Kappa statistic[22]. The magnitude of change assessed by TSDB is considered significant if at least two consecutive data points fall above or below two standard deviations from the mean of the previous phase[16,22]. The CL compares the rate of change between consecutive phases through the determination of a trend line. Differences in the tendency of change of performance with the introduction of a new study phase is tested according to the proportion of data points above and below the trend line of the previous phase with the Binomial test[16,22]. Visual analysis and TSDB are appropriate when there are no significant trends, as tested with the C-Statistics and auto-correlation in baseline data. Moreover, variability of baseline phase was evaluated by coefficients of variation calculated for each studied variable[22]. The stability of data points during intervention phase was assessed by regression analysis[22]. The Statistical Package for Social Sciences software (SPSS, Chicago, IL, USA) version 13.0 was used and level of significance was set at $p < 0.05$.

RESULTS

Subject

By the inclusion in the study, the participant had received five years of regular medical treatment since he was diagnosed with COPD and there was no change in his medications during all the study period. He used the following medications throughout the study period: Foraseq® 12/400mcg, Duovent® 0,04/0,1mg/dose and Hydrochlorothiazide® 25 mg. His grade of dyspnea sensation according to the modified MRC was 1 and his adjusted score of activity in the HAP was 70 (moderately active).

Training Program

The adherence to the treatment was 100%, which corresponded to 36 sessions in the total. The intensity of training was 55 watts and the participant reached 30 minutes of cycling at the training work rate in the 18th session, keeping this duration until the end of the treatment (Figure 1).

Cardiopulmonary exercise testing responses

The quality of the fifth test of baseline phase was considered inadequate and, consequently, this test was not considered in data analyses. Considering the remaining tests used in the analyses, the motivation to interrupt them was breathlessness in six and a combination of this symptom and lower-limb fatigue in five. The autocorrelation analyses of data resulted in coefficients not statistically significant for all studied variables, showing that there was not serial dependency. With respect to the coefficients of variation, all of them were less than 15% for all variables. Kappa values were 1 for all variables except for WR and isowork *f*, ranging between 0.44 and 1 and -0.77 and 1, respectively.

Table 1 shows the results of visual analysis and statistical methods (TSDB and CL) for the comparison of peak exercise variables between phases A and B. It was observed significant increase in WR, $\dot{V}CO_2$ and $\dot{V}E$ in phase B compared to phase A, as demonstrated by visual analysis and CL. Regarding the data tendency, all evaluators classified all peak exercise variables as stable in both phases of the study.

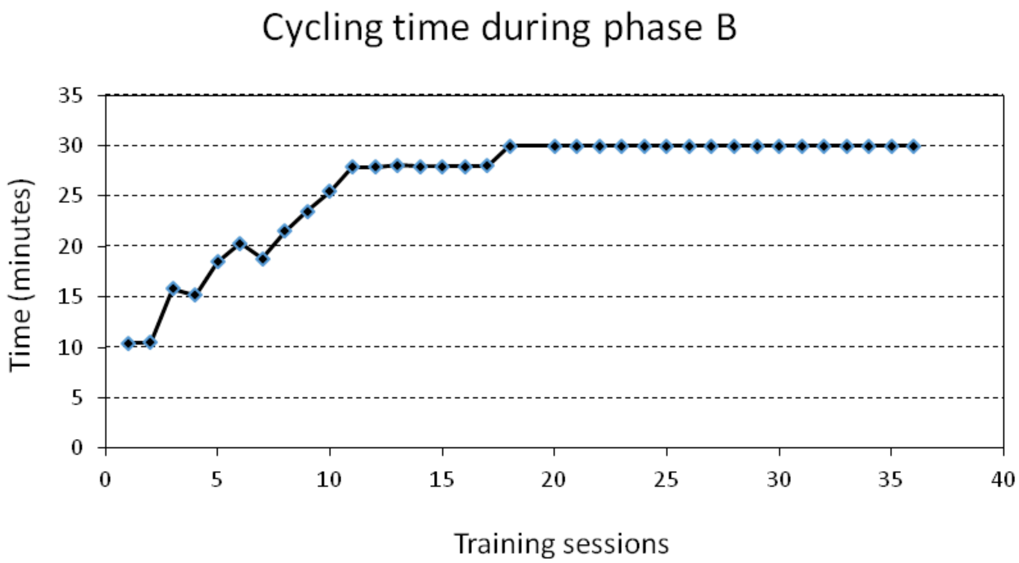

Figure 1: Cycling time at the target intensity 55 watts and during phase B (intervention)

Table 1: Results of visual analysis and statistical methods for peak variables

Peak variables	Changes in tendency (VA)		Changes in magnitude (VA)	Two- standard deviation band	Celeration line
	Phase A	Phase B			
WR	S (3)	S (3)	⇑ (2)	*ns*	⇑
$\dot{V}O_2$ **(ml/min)**	S (3)	S (3)	⇑ (3)	*ns*	*ns*
$\dot{V}CO_2$ **(ml/min)**	S (3)	S (3)	⇑ (3)	*ns*	⇑
$\dot{V}E$ **(l/min)**	S (3)	S (3)	⇑ (3)	*ns*	⇑

CL: Celeration Line; ⇑increase in phase B related to phase A; *ns*: non-statistically significant; ( ) number of experts who agreed in a specific aspect of visual analysis; S: stable; VA: Visual Analysis; $\dot{V}E$: minute ventilation; $\dot{V}CO_2$: carbon dioxide output; $\dot{V}O_2$: oxygen uptake; WR: work rate; *p < 0.05.

Table 2: Results of visual analysis and statistical methods for isowork variables

Isowork variables	Changes in tendency (VA)		Changes in magnitude (VA)	Two - standard deviation band	Celeration - line
	Phase A	Phase B			
$\dot{V}O_2$ **(ml/min)**	A (3)	D (3)	_	⇓	*Ns*
$\dot{V}E$ **(l/min)**	A (3)	D (3)	_	*ns*	⇓
Vt (l)	A (3)	A (3)	I	*ns*	⇑
f **(irpm)**	D (3)	D (3)	I	⇓	*Ns*
Perceived exertion	A (3)	D (3)	_	⇓	⇓
HR (bpm)	S (3)	S (3)	⇓ (3)	⇓	⇓
SpO_2 (%)	D (3)	A (3)	_	⇑	*Ns*

A: Acceleration; D: Deceleration; *f*: respiratory frequency; HR: heart rate; I: inconclusive; and ⇑ increase ⇓ and decrease in phase B related to phase A, respectively; __ non-applicable; *ns*: non-statistically significant; ( ) number of experts who agreed in a specific aspect of visual analysis; S: Stable; SpO_2: peripheral oxygen saturation; VA: Visual Analysis $\dot{V}E$: minute ventilation; $\dot{V}O_2$: oxygen uptake; Vt: tidal volume.*$p < 0.05$.

Table 2 shows the results of visual analysis and statistical methods (TSDB and CL) for the comparison of isowork variables between phases A and B. The $\dot{V}O_2$, $\dot{V}E$, perceived exertion and HR presented significant decrease while SpO_2 increased significantly in the intervention phase, as demonstrated by visual analysis and TSDB and/or CL. All these variables, except HR that was stable in phases A and B, showed changes in tendency: $\dot{V}O_2$, $\dot{V}E$ and perceived exertion were accelerating (or increasing) in phase A and decelerating or reducing in phase B while SpO_2 was decelerating in phase A and accelerating in phase B. These results were confirmed by at least one statistical analysis. The results of visual analysis for Vt and *f* regarding the change in magnitude were inconclusive because at least two evaluators considered that was not possible to establish such change. The responses of WR, $\dot{V}O_2$ and $\dot{V}E$ at peak of exercise and $\dot{V}O_2$, $\dot{V}E$, HR, SpO_2 and perceived exertion at isowork demonstrated significant increase or decrease in the intervention phase shown by visual analysis and at least one statistical method can be seen in Figure 2.

The main results related to the initiation of changes in exercise capacity in phase B was that isowork variables ($\dot{V}O_2$, $\dot{V}CO_2$, $\dot{V}E$, perceived exertion and SpO_2) started showing changes in the 10^{th} week of the study which corresponded to the fourth week of the intervention phase. Kappa results were 1 for all variables, demonstrating absolute agreement between the three assessors for these analyses. Table 3 shows F values and associated *p*, regression coefficients (β), coefficients of determination (r^2) and standard error of the estimate (SEE) resulting from regression analysis of intervention phase data. None of peak exercise variables associated significantly with time variable. Otherwise, with respect to isowork variables, it was observed significant linear association between $\dot{V}O_2$, Vt, *f*, and SpO_2 and time variable, with increase of Vt and SpO_2 and decrease of $\dot{V}O_2$ and *f* throughout phase B.

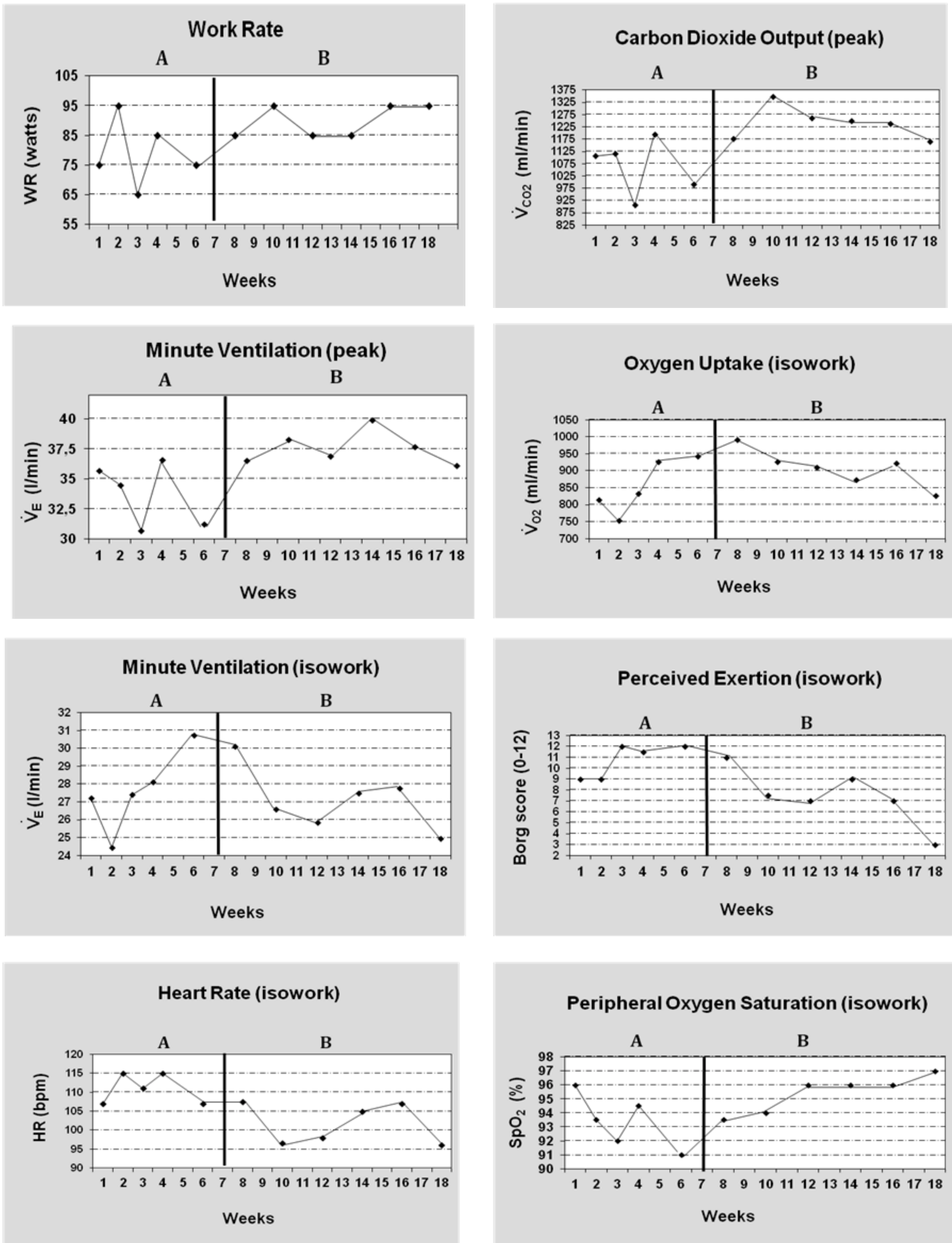

Figure 2: Response of peak and isowork variables in phases A and B

Furthermore, $\dot{V}E$, perceived exertion and HR showed cubic significant relationship with time variable. Moreover, $\dot{V}E$ and perceived exertion decreased during the phase B, as showed by visual analysis.

Table 3: Results of regression analysis for isowork variables in phase B

Isowork variables	F*	β1	β2	β3	r²	SEE
$\dot{V}O_2$ **(ml/min)**	10 (0.03)*	-12.55	___	___	0.72	33.18
$\dot{V}E$ **(ml/min)**	57.1 (0.01)*	- 4.80	0.87	- 0.05	0.98	0.30
Vt (ml)	9.82 (0.03)*	17.8	___	___	0.71	47.64
f **(irpm)**	19.9 (0.01)*	- 0.679	___	___	0.83	1,27
Perceived exertion	21.5 (0.04) *	- 4.63	0.89	-0.05	0.97	0.73
HR (bpm)	543.7 (0.002)	-16.5	3.32	-0.18	0.99	0.30
SpO₂ (%)	23.9 (0.008)*	0.336	___	___	0.86	0.57

β: regression coefficients; *f*: respiratory frequency; HR: heart rate; ___: non-applicable; SEE: standard error of the estimate; SpO_2: peripheral oxygen saturation; ( ): *p* values associated to F parameter; r^2: coefficient of determination $\dot{V}E$: minute ventilation; $\dot{V}O_2$: oxygen uptake; Vt: tidal volume. *$p < 0.05$

DISCUSSION

To the best of our knowledge, it was the first study assessing over time, in short and regular periods, the effects of lower-limb endurance training in Chronic Obstructive Pulmonary Disease. The patient improved his exercise capacity after endurance training and this result was consistent with studies investigating exercise training in patients with COPD[23-25]. Changes in some isowork variables initiated in the fourth week of the intervention phase and continued, without stabilization, until the end of the training program.

Changes in exercise capacity observed in the fourth week of intervention are, in accordance with Skumlien *et al.*[26]. Other studies that assessed effects of rehabilitation programs lasting three weeks and including lower-limb endurance training also verified improvement in exercise capacity in patients with COPD[27-29].

Our finding of progressive improvement in some variables reflecting exercise tolerance is partially confirmed by the study of Rossi *et al.*[8] who verified improvement in exercise capacity in patients with chronic airway obstruction after the 10th and 20th sessions of a multidisciplinary rehabilitation program carried out three times per week. However, changes in exercise capacity were significantly higher after the 20th session. On the other hand, Green *et al.*,[7] and Sewell *et al.* [9], observed similar gains in exercise tolerance when they compared multidisciplinary rehabilitation programs lasting four and seven weeks. But these authors used the incremental shuttle-walking test to assess exercise capacity and did not evaluated variables obtained from cycle ergometer incremental tests.

In the present study, a patient with severe COPD changed his exercise capacity, which was verified by variables at isowork condition, in the fourth week of the training. These results reinforce findings from other studies[8, 28, 29] showing that rehabilitation programs lasting short periods of time can produce significant physiological gains as well as the British Thoracic Society[11] recommendation that programs with a course of duration of four weeks at the minimum, carried out two to five times per week, are associated with training effects. A significant aspect of those findings refers to the fact that shorter programs are less expensive and allow more patients to experience rehabilitation[9, 30]. However, further studies should be designed in order to address the cost-benefit ratio of programs with different duration.

Furthermore, it is important to consider that despite the physiological gains observed in the fourth week of training, these changes continued until the end of the intervention, as demonstrated by visual analysis and regression analysis. According to Troosters *et al.*[10,30], one of the goals of rehabilitation programs should be to produce the maximum possible benefit to patients and longer duration programs than that necessary for the occurrence of physiological effects appear to be beneficial. This may be associated with the fact that behavioral changes and health related quality of life improvements appear to require longer time[7,30]. However, the study of Sewell *et al.*[9] showed that patients who underwent four or seven-week programs did not present significant differences in improvement of health related quality of life. Thus, further studies seem necessary to clarify whether longer programs produce greater physiological gains and other benefits.

One limitation of the present study is the generalization of the findings to the patients with COPD with characteristics different to those presented by the patient evaluated. In this way, it would be interesting to replicate this design with patients with different ages, GOLD stages, and dyspnea grades to increment the external validity of the findings.

We believe that the results of this study can contribute to improve the understanding of the duration (weeks of training) of the rehabilitative exercise training program, a topic frequently discussed but poorly investigated[30]. Moreover, highlighted by Troosters *et al.*[10], the impact of varying duration of pulmonary rehabilitation programs has been investigated only at a group rather than at the individual patient level: at a group level longer programs may be beneficial; however, rehabilitation in unlikely to produce optimal results after a given number weeks in every patient and for every outcome. Therefore, the present study can provide some guidance to the utilization of the single-subject experimental design to further investigate this question.

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