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Are thirty minutes of rest between two 6-Minute Walk Tests enough for cardiovascular and symptomatic recovery for patients with chronic obstructive pulmonary disease?

Trinta minutos de repouso entre dois testes de caminhada de 6 minutos são suficientes para recuperação cardiovascular e sintomatológica em pacientes com doença pulmonar obstrutiva crônica?

¿Son suficientes treinta minutos de descanso entre dos test de caminata de 6 minutos para recuperación cardiovascular y de síntomas en pacientes con enfermedad pulmonar obstructiva crónica?

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ABSTRACT | Two 6-Minute Walk Tests (6MWT) are required to evaluate functional capacity of exercise in patients with Chronic Obstructive Pulmonary Disease (COPD). Despite the fact that the American Thoracic Society (ATS) has proposed a one-hour interval between two tests, it is unknown whether a shorter period could be used for the normalization of physiological variables. We aimed to verify that an interval of 30 minutes of rest between two 6MWT is sufficient for cardiovascular and symptomatic variables to return to their basal levels. Two hundred and fifteen patients with COPD (121H, 66±8 years; FEV_1: 44 [32-57]% predicted) performed two 6MWT with a thirty-minute interval between them. Before and after the tests, we measured Blood Pressure (BP), Heart Rate (HR), peripheral oxygen saturation (SpO_2), degree of dyspnea, and fatigue. Patients walked the longest distance in the second test (6MWT1: 450 [390-500]m vs 6MWT2: 470 [403-515]m; p<0.0001). The initial HR was greater in the second 6MWT (initial HR 6MWT1: 83 [73-91]bpm *vs* 6MWT2: 83 [75-93]bpm; p=0.001). Dyspnea and fatigue were lower before the second test (initial Borg dyspnea 6MWT1: 0.5 [0-2]m *vs* 6MWT2: 0 [0-2]; p = 0.0006 and initial Borg fatigue 6MWT1: 0 [0-2]m *vs* 6MWT2: 0 [0-2]; p = 0.007). There were no differences regarding the BP and the SpO_2 (p>0.05 for all). Although there are statistically significant differences in initial HR between the first and second test, this finding does not seem to be clinically relevant. Therefore, thirty minutes of rest between two 6MWT are sufficient for cardiovascular and symptomatic recovery in patients with COPD.

Keywords | Exercise; Pulmonary Disease, Chronic Obstructive; Rest.

RESUMO | Dois testes da caminhada de 6 minutos (TC6min) são necessários para avaliação da capacidade funcional de exercício em pacientes com doença pulmonar obstrutiva crônica (DPOC). Apesar de a American Thoracic Society (ATS) preconizar um intervalo de 1 hora entre dois testes, não se sabe se um período menor poderia ser utilizado para normalização das variáveis fisiológicas. O objetivo foi verificar se o intervalo de 30 minutos de repouso entre dois TC6min seria suficiente para que as variáveis cardiovasculares e sintomatológicas retornassem aos valores basais. Duzentos e quinze pacientes com DPOC (121H, 66±8 anos; VEF_1: 44[32-57]% previsto) realizaram dois TC6min com intervalo de 30 minutos entre eles. Foram mensuradas antes e após os testes, pressão arterial (PA), frequência cardíaca (FC), saturação periférica de oxigênio (SpO_2) e grau de dispneia e fadiga. Os pacientes caminharam maior distância no segundo teste (TC6min1: 450 [390-500]m *vs* TC6min2: 470 [403-515]m; p<0,0001). A FC inicial foi maior no segundo TC6min (FC inicial

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TC6min1: 83 [73-91]bpm *vs* TC6min2: 83 [75-93]bpm; p=0,001). Dispneia e fadiga foram menores antes do segundo teste (Borg dispneia inicial TC6min1: 0,5 [0-2] *vs* TC6min2: 0 [0-2]; p=0,0006 e Borg fadiga inicial TC6min1: 0 [0-2] *vs* TC6min2: 0 [0-2]; p=0,007). Não houve diferenças quanto à PA e SpO_2 (p>0,05 para todos). Embora haja diferença estatisticamente significante na FC inicial entre o primeiro e segundo teste, tal achado não parece ser clinicamente relevante. Portanto, trinta minutos de repouso entre dois TC6min são suficientes para recuperação sintomatológica e cardiovascular em pacientes com DPOC.

Descritores | Exercício; Doença Pulmonar Obstrutiva Crônica; Descanso.

RESUMEN | Dos test de caminata de 6 minutos (TC6min) son necesarios para que se evalúe la capacidad funcional de ejercicio en pacientes con enfermedad pulmonar obstructiva crónica (EPOC). Aunque la American Thoracic Society (ATS) sugiere 1 hora de intervalo entre dos test, todavía se desconoce si puede utilizarse un periodo menor para normalización de las variables fisiológicas. En este estudio se comprobó que es suficiente el intervalo de 30 minutos de descanso entre dos TC6min para que las variables cardiovasculares y de síntomas vuelvan a sus valores de referencia. El estudio se llevó a cabo con 215 pacientes con EPOC (121H, 66±8 años: VEF_1: 44[32-57]% previsto), que hicieron dos TC6min con intervalos de 30 minutos. Antes y después de los test se midieron la presión arterial (PA), la frecuencia cardíaca (FC), la saturación de oxígeno (SpO_2) y el grado de disnea y de cansancio. Los pacientes caminaron una distancia más grande en el segundo test (TC6min1: 450 [390-500]m *vs* TC6min2: 470 [403-515]m; p<0,0001). La FC fue mayor en el segundo TC6min (FC inicial TC6min1: 83 [73-91]lpm *vs* TC6min2: 83 [75-93]lpm; p=0,001). La disnea y el cansancio fueron menores antes del segundo test (Borg disnea inicial TC6min1: 0,5 [0-2] *vs* TC6min2: 0 [0-2]; p=0,0006 y Borg cansancio inicial TC6min1: 0 [0-2] *vs* TC6min2: 0 [0-2]; p=0,007). En cuanto a la PA y la SpO_2 no hubo diferencias significativas con p>0,05 para todos. Aunque tenga diferencia estadística significante en la FC inicial entre el primer y el segundo test, el resultado no es clínicamente relevante, por lo tanto, los 30 minutos de descanso entre dos TC6min son suficientes para la recuperación cardiovascular y de síntomas en pacientes con EPOC.

Palabras clave | Ejercicio; Enfermedad Pulmonar Obstructiva Crónica; Descanso.

INTRODUCTION

According to the Global Initiative for Chronic Lung Disease (GOLD), the Chronic Obstructive Pulmonary Disease (COPD) is a preventable and treatable disease characterized by the persistent obstruction to the airflow that is usually progressive. It is associated with a chronic inflammatory response in the airways and in the lungs caused by harmful particles and gases[1]. In addition to the pulmonary component, the disease presents systemic consequences such as peripheral muscle weakness, worsening of quality of life, weight loss, and malnutrition. These disorders are related to the restriction in the ability of performing physical exercises and daily activities of these individuals[2].

Considering the systemic changes caused by the disease, the assessment of the ability to exercise becomes of extreme importance in this population, and may be accomplished through laboratory tests and field trials. The Cardiopulmonary Exercise Testing (CPET) is considered the gold standard for the assessment of exercise capacity, allowing the identification of causes of intolerance to physical efforts[3]. Through this test it is possible to obtain direct measurement of gas exchange (oxygen consumption – VO_2 and elimination of carbon dioxide – VCO_2), maximum heart rate (maxRH), among other. However, specific equipment are required to complete the CPET such as treadmill, or cycle ergometer, gas analyzer, besides a trained staff to deal with any alteration that may occur[4]. Therefore, because of the difficulties in conducting the CPET, some field trials are being developed, such as the Incremental Shuttle Walking Test (ISWT) and the 6-Minute Walk Test (6MWTmin), which has been often used[5].

The 6-Minute Walk Test (6MWT) is the most commonly used test in the field of pulmonary rehabilitation, as it is practical, simple, easy to use, of low cost, and highly reproducible in clinical practice[6]. With this test it is possible to assess the functional capacity of exercise and get an integrated response of physical (pulmonary and extra-pulmonary) and psychological factors[5]. According with a study by Hernandez et al., the reproducibility of the 6MWT in patients with COPD was assessed in two tests carried out in subsequent days. The 6MWT has shown to be reproducible. However, the patients have walked a statistically higher distance in the second test, which also confirms the learning effect, emphasizing the need to carry out two tests[7].

For the normalization of physiological variables, the American Thoracic Society (ATS) recommends an interval of at least an hour between the two 6MWT[5]. However, there are still no research able to prove if intervals smaller than an hour are enough for the normalization of physiological variables to its basal state (or pre-test) in patients with COPD. Thus, it is necessary to investigate shorter intervals between the two tests for better clinical convenience. Smaller intervals are advantageous for patients who require shorter times of evaluation, as for evaluator that would have more available time to carry out other evaluations and treatments.

Therefore, the aim of this study was to verify the hypothesis that an interval of 30 minutes of rest between two 6MWT is sufficient for cardiovascular and symptomatic variables to return to their basal levels in individuals with COPD.

METHODOLOGY

We have conducted a cross-sectional study in Pulmonary Physiotherapy Research Laboratory (LFIP) at the Health Sciences Center (CCS) at the University Hospital of Londrina (HU) of the Universidade Estadual de Londrina (UEL) and the Center for research in Health Sciences (CPCS) of Universidade Norte do Paraná (UNOPAR).

To be included, all patients must have confirmed diagnosis of COPD, according to the criteria of the Global Initiative for Lung Disease[1] such as the absence of exacerbations in the last three months, the absence of comorbidities that could interfere in tests' performance, and have not practiced any kind of regular exercise in the last year. The criteria of exclusion of the study were: inability to perform the test, the individual's choice of not continuing the treatment at any moment of the protocol or the completion of only one 6MWT. The Committee for Ethics in Research Involving Humans of the Universidade Estadual de Londrina (CEP/UEL 173/2012) and of the Universidade Norte do Paraná (PP0033/11) have approved this study, and all patients signed a free and informed consent form.

All individuals were assessed at the time of admission to a pulmonary rehabilitation program and underwent a pulmonary function test through spirometry using a portable spirometer (Spiropalm®; COSMED, Italy). We carried out the technique according to the international guidelines of Miler et al. with the determination of the Forced Expiratory Volume (FEV_1) in one second, Forced Vital Capacity (FVC) and FEV_1/ FVC index. We performed the minimum three test repetitions by using the values of reference for the Brazilian population proposed by Pereira et al.[8].

Individuals also had their exercise capacity assessed through the 6MWT. We performed the test according to the international recommendations[5] in a corridor of 30 meters. In addition to conducting two tests with an interval of 30 minutes between them, we have also monitored all patients in relation to dyspnea and fatigue (through a modified Borg scale)[9], Blood Pressure (BP), Heart Rate (HR) and Peripheral Oxygen Saturation (SpO_2) before and after the test, and during recovery (two minutes from the end of the test). The same evaluator conducted the two 6MWT at the same time of the day. The reference value by Britto et al.[10] was used.

For the statistical analysis we used the GraphPadPrism software version 6.0. We have verified data normality by the Shapiro-Wilk test and comparisons of variables by paired t-test or by Wilcoxon test. By calculating the power of the sample through the Power & Sample Size Calculation program, we have found the value 1.0 using the average delta of the distance traveled between the two tests, which was 17.04 m, and a standard deviation of 38.32 m with α = 0.05 and n = 200 patients. To evaluate Cohen's d effect size of the analyzed variables between the two tests, we used the GPower 3.1 program. The statistical significance adopted was $P<0.05$. For the analysis, we excluded the outliers from the sample. Outliers are defined here as patients who showed the value of distance traveled longer or shorter than the mean value plus or minus two standard deviations.

RESULTS

Initially, we evaluated 223 patients, considering that 23 individuals were excluded from the study. The reasons for their exclusion are illustrated in Figure 1. The final analysis was performed with 200 patients diagnosed with COPD (121H, 66±8 years, BMI: 25[21-29] $kg.m^{-2}$, FEV_1: 44[32-56] % predicted).

The initial variables in the first and second 6MWT are listed in Table 1. Patients walked the longest distance in the second 6MWT, and when the cardiovascular variables were analyzed, the HR was bigger before the second 6MWT, when compared to the first (Figure 2A). Additionally, the calculation of the effect size have shown that, despite the HR being bigger before the 6MWT 2, the value obtained was 0.13. Symptoms as dyspnea (Borg D) and lower limbs

fatigue (Borg F) were lower before the second test (Figure 2B). No statistically significant difference was found in the comparison of initials PA and SpO_2 between the two tests.

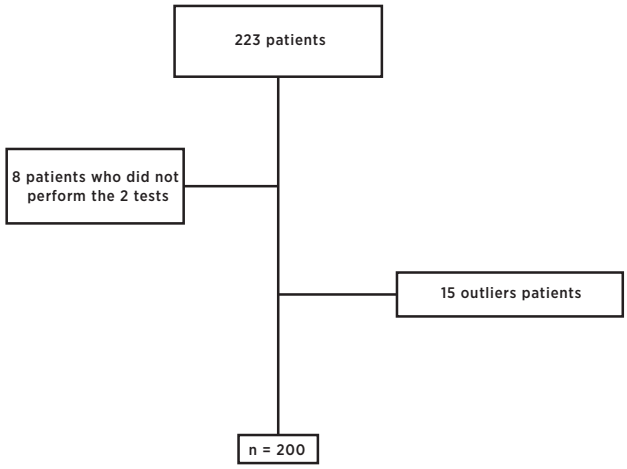

Figure 1. Flowchart of patients included in the study

When separated by disease severity according to the GOLD classification in GOLD group I and II (GOLD I: FEV_1 >80% predicted; GOLD II: 50% < FEV_1 <80% predicted) and groups GOLD III e IV (GOLD III: 30% < FEV_1 <50% predicted; GOLD IV: FEV_1< 30% predicted) (Table 2), both in the most severe and in the least severe cases have traveled a longer distance in the second 6MWT, despite presenting HR bigger before the second test. About the symptoms, the most severe patients have shown smaller values of Borg dyspnea and fatigue before the second test. There was no statistically significant difference in the comparison of Borg D and Borg F between the first and the second test in less severe patients. The figure of Bland-Altman illustrates the performance of each patient in each test (Figure 3), and when the proportions were analyzed, it was possible to verify that there was no difference in tests' performance according to disease severity (p=0.24).

We calculated the maximum heart rate (maxHR) considering individuals who used or not β-blocker drugs. For the group of patients who did not need to make use of medicines, we used the formula by Tanaka et al. (208 – 0.7* age)[11], and to the other group that needed to use this medicine, we used the formula of Brawner et al. (164 – 0.72* age)[12]. Patients achieved a larger maxHR in the second 6MWT than in the first test (Table 1). In relation to the analysis of heart rate variation (ΔHR), we have not found statistically significant difference between the two tests (ΔHR 6MWT1: 25[15-35] bpm *vs* ΔFC 6MWT2: 24 [16-35]bpm; *P*=0.63). In addition, we did not verify statistical significance when the variation of other outcomes (ΔSpO_2, ΔBorg D, ΔBorg F, ΔPAS, and ΔPAD) was compared between the first and second test (P> 0.05 for all).

Table 1. Comparison of variables between the first and the second 6MWT

	6MWT1	6MWT2	P
6MWT (m)	450 [390 - 500]	470 [403 – 515]	<0.0001
HR pre-test (bpm)	83 [73 – 91]	83 [75 – 93]	0.001
Borg D pre-test	0.5 [0 - 2]	0 [0 - 2]	0.0006
Borg F pre-test	0 [0 - 2]	0 [0 - 2]	0.007
SBP pre-test (mmHg)	130 [120 - 140]	120 [120 - 140]	0.26
DBP pre-test (mmHg)	80 [70 - 80]	80 [70 - 80]	0.25
SpO2 pre-test (%)	95 [93 - 96]	95[94 - 96]	0.5
% maxHR	67 [70 - 73]	68 [61 - 75]	0.0052
DP	9720 [8360 - 11340]	765900 [629970 - 963340]	<0.0001

Variables are presented as median and interquartile range [25-75%]. 6MWT: Six-minute walk test; HR: heart rate; Borg D: Borg dyspnoea; Borg F: Borg fatigue; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; SpO_2: Peripheral oxygen saturation, % maxHR: maximum percentage of heart rate, DP: double product

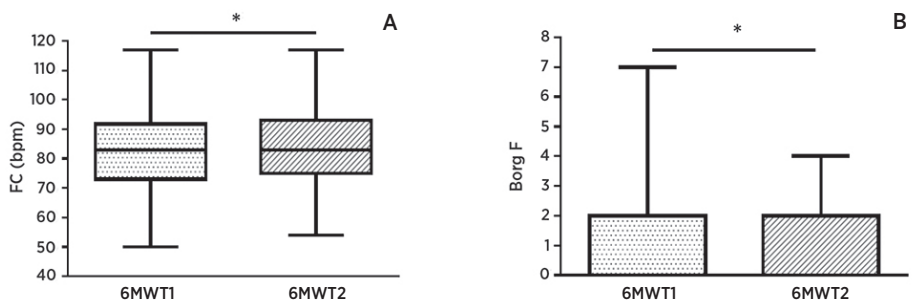

Figure 2. Variables are presented as median and interquartile range [25-75%]. Comparison of HR pre-test (Figure A) and Borg Fatigue pre-test (Figure B) between the first and the second 6MWT (*P≤0.001)

Table 2. Comparison of variables between the first and the second 6MWT according to the severity of the disease

	GOLD I and II (n=77)			GOLD III and IV (n=123)		
	6MWT1	6MWT2	P	6MWT1	6MWT2	P
6MWT (m)	456±71	475±69	<0.0001	428[373-484]	457[383-501]	<0.0001
HR pre-test (bpm)	81±13	83±12	0.01	83±13	85±12	0.03
Borg D pre-test	0[0-1.5]	0[0-1]	0.26	1[0-2]	0.5[0-2]	0.0007
Borg F pre-test	0[0-2]	0[0-2]	0.65	0[0-2]	0[0-2]	0.003
SBP pre-test (mmHg)	130[120-140]	120[118-130]	0.18	125[120-140]	130[120-140]	0.65
DBP pre-test (mmHg)	80[70-80]	80[70-80]	0.65	80[70-80]	80[70-80]	0.26
SpO2 pre-test (%)	96[94-97]	96[95-97]	0.89	95[92-96]	95[93-96]	0.44
% maxHR	67[59-73]	68[60-75]	>0.05	67[60-74]	68[60-75]	0.10

Variables are presented as mean ± standard deviation, and median and interquartile range [25-75%]. 6MWT: Six-minute walk test; HR: heart rate; Borg D: Borg dyspnea; Borg F: Borg fatigue; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; SpO_2: Peripheral oxygen saturation; % maxHR: maximum percentage of heart rate; GOLD I (n=2): FEV_1 > 80% predicted; GOLD II (n=75): 50% < FEV_1 <80% predicted; GOLD III (n=84): 30% < FEV_1 <50% predicted; GOLD IV (n=39): FEV_1 <30% predicted

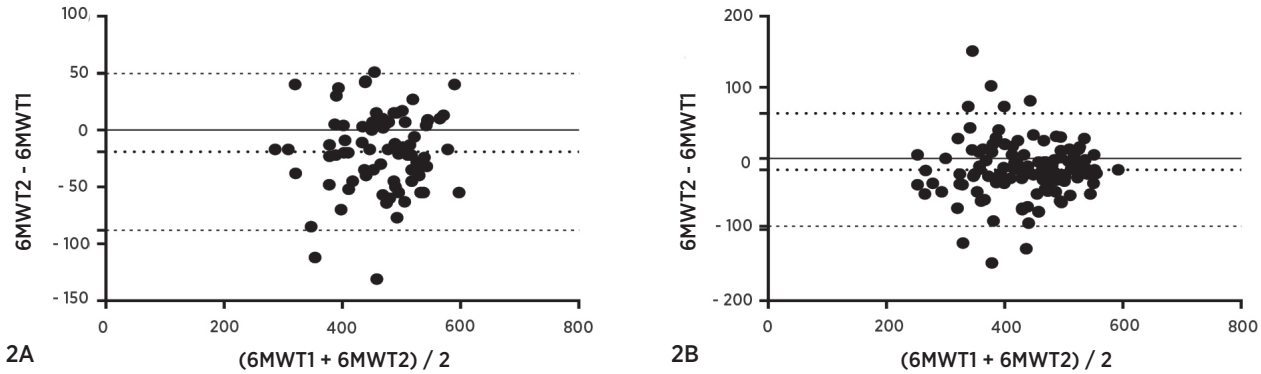

Figure 3. Bland-Altman chart with the difference between the two 6MWT and the average of values of the 6MWT1 and the 6MWT2 in patients classified as GOLD I and II (Figure 2A) and GOLD III and IV (Figure 2B)

To verify the estimate of cardiac work, we calculated the double product (HR*PAS) and thus, it was possible to observe higher values in the first 6MWT (Table 1).

DISCUSSION

In this study, patients traveled a longer distance in the second test accompanied by a higher HR pre-test, although with small values of effect size. We have observed that symptomatology was lower before the second test, and that no statistically significant differences were found regarding BP and SpO_2. When patients were separated into groups by disease severity according to the GOLD classification, both groups of least severe diseases and of most severe diseases have continued showing longer traveled distance and higher HR pre-test in the second test. In the analysis of the symptomatic variables, the most severe patients have shown a reduction before the second test, while no statistically significant difference was found in the symptoms of the group of least severe diseases. The BP and SpO_2 pre-test of both groups were similar in the first and second 6MWT.

Patients possibly traveled a longer distance in the second test because of the learning effect already confirmed earlier. In the study of Hernandes et al., 1514 patients COPD diagnosed with moderate to severe obstruction, participated of two 6MWT in two subsequent days, and 82% of patients have walked more in the second test, with an average of 27 m further from the first[7]. In this sample, patients increased on average 20 metres in the second 6MWT in comparison with the first, which is also seen in Sciurba et al.[13].

There was a statistically significant difference between the basal HR of the first and of the second test, showing that thirty minutes of rest between the two tests are not statistically sufficient to recover HR to their pre-test values. Lacasse et al. claim that individuals with COPD have late HR recovery after exercise when compared to healthy individuals.

The authors propose that cardiovascular problems are present in patients with COPD, and systemic inflammation has been considered as a possible explanation for the risk of cardiovascular changes[14]. Another finding to be considered is the influence of age in HR, which is confirmed by Zhang, who evaluated the autonomic activity of individuals of 10 to 80 years, finding a reduction in the increase of autonomic activity, and a reduction in HR with aging[15]. Both studies have mentioned factors that influence cardiovascular activity, so that it is possible to consider that, such factors, among others, influence the cardiovascular variable even after an interval of 30 minutes. Although a statistically significant difference was observed between the basal HR of the first and of the second test, the calculation of effect size of HR was of S=13, and does not represent any classification for the effect size, which allows us to state that this significance found between the two tests is clinically irrelevant.

Still on cardiovascular activity, the double product (DP) is a variable that correlates very well with oxygen uptake by the myocardium, and it is, therefore, a reliable indicator of heart work during the exercise[16]. In the study of Ribeiro et al. on healthy subjects, there was a greater DP in the second test accompanied by a maxHR range greater than 90% of the predicted in the Incremental Shuttle Walking Test[17]. Similarly, in our analysis, patients had a statistically significant increase in the DP in the second test, accompanied by an increase in maxHR in relation to the first test, which is expected since the individuals have shown better performance in the second test with a longer distance traveled. Although the difference between the DP and the maxHR of the tests has been checked, when we calculated the variation (ΔHR), no difference between the two tests was found. It probably could have occurred because the second test started with a FC slightly greater regarding the baseline of the first test.

Despite the inability of performing an analysis in which there is a comparison between tests at intervals of 30 minutes and 1 hour, we can say that even without HR's full recovery, it was possible to obtain a better performance in the second test in relation to the first. However, it would be safe to say that there was no prejudice in the second test's performance or that it would be possible to achieve higher performances.

The 30-minute interval was enough for symptomatic variables and, moreover, it was found that patients began the second test with less severe symptoms in relation to the first test. When separated by disease severity (GOLD I and II *versus* GOLD III and IV), the group of most severe disease has presented smaller symptomatic variables before the second test in relation to the first test. No statistically significant difference was verified concerning symptomatic variables between the two tests in the group of less severe diseases. We can consider the hypothesis that, in more severe cases, patients are used to the disease's symptoms, not being so affected by dyspnea and fatigue, which may explain the decrease in these symptoms' report before the second 6MWT. Cooper investigated the specificity of training that generates desensitization of dyspnea in patients with COPD. In his study, patients were evaluated regarding dyspnea after the completion of the cycle endurance test. Patients presented desensitization of dyspnea after the repetition of the 6MWT, but not after the endurance test, which may indicate that the desensitization happens mainly in certain situations[18]. In another study, Belman et al. aimed to evaluate the variability in the measurement of dyspnea in COPD; patients' maximum capacity was evaluated by using an incremental treadmill test until they felt limited by symptoms. At the interval of the test, they were asked about dyspnea through a modified Borg scale to record the maximum sensation of dyspnea, so that they can consider this feeling at other times. Within ten days, four 6MWT were carried out in the treadmill with speed of 95% of the VO_2max. By the end of the test, all patients reported their degree of dyspnea, which during the period of four days was being progressively reduced. The authors suggest desensitization is a process of reducing the fear and the insecurity in relation to symptoms[19].

In our study, it is possible to highlight some positive points such as the sample size, since, although it was not calculated, it was enough to find statistically significant differences in the variables studied (power of 1.0). We adopted a certain methodological accuracy in the study, since we did not allow variability of evaluators between the two tests conducted with each patient, also ensuring that all tests were carried out at the same time of day. We also highlight that the relevance of the study may contribute to clinical practice in what concerns the time for rest during the evaluation of the functional capacity of exercise for patients with COPD. Despite the fact that the range of 30 minutes between the two 6MWT has already

been described[20], until recently what was encouraged was to wait for a period of one hour among tests[5]. In this sense, our results strengthen what is proposed by the new Statement for the 6MWT for patients with chronic pulmonary diseases, which suggests 30-minute intervals between the two tests[21].

Other limitations, among some already mentioned, can be observed in this study, such as the inability to analyze different recovery time intervals between two 6MWT, once we cannot state that there was no prejudice in the second test. Additionally, the fact that this study is of transversal character did not allow the analysis of cause, effect or determinants of the HR recovery. Thus, we suggest that further studies are carried out to verify these variables after an intervention, such as physical training.

CONCLUSION

Although there are statistically significant differences in initial HR between the first and the second test, such finding does not seem to be clinically relevant. Therefore, we consider a period of 30 minutes of rest between the two 6MWT sufficient for cardiovascular and symptomatic recovery for patients with COPD.

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