Interval training induces clinically meaningful effects in daily activity levels in COPD

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Take home message
12 weeks of high-intensity interval exercise training induces clinically meaningful effects on the amount and intensity of daily activities in COPD.

To the Editor,

Mounting evidence suggests that Daily Activity Levels (DAL) in patients with Chronic Obstructive Pulmonary Disease (COPD) are markedly low compared to healthy age-matched individuals and are associated with poorer health status and prognosis [1]. COPD severity negatively impacts on DAL since patients with low DAL experience greater ventilatory, central hemodynamic and peripheral muscle oxygenation constrains during activities of daily living when compared to more physically active counterparts [2,3]. Although exercise training as part of Pulmonary Rehabilitation (PR) has shown to mitigate the aforementioned physiological constraints [4], there is no evidence of clinically meaningful improvement on DAL following PR [5] (manifested by a mean increase of at least 1000 steps/day [6]). This has been attributed to methodological shortfalls such as lack of adequately controlled studies, small sample size, short duration of PR programmes, application of non-validated for COPD patients activity monitors [5] and insufficient exercise intensities to induce true physiological training effects. Interval exercise training has been shown to allow application of intense loads to peripheral muscles that induce substantial physiological effects manifested by mitigation of respiratory and central hemodynamic limitations and partial restoration of peripheral muscle dysfunction in patients with diverse COPD severity [7,8]. In this context it is reasoned that application of this training modality would allow transfer of the aforementioned physiological benefits into clinically meaningful improvements in DAL. Accordingly, the purpose of this randomized controlled study was to investigate the effect of a 12-week high-intensity interval exercise training programme on DAL in addition to usual care in patients with COPD.

The study was approved by the University Hospital Ethics Committee (Protocol ID: 18367). One-hundred fifty (150) consecutive patients with COPD were screened and referred for an outpatient 12-week pulmonary rehabilitation programme between September 2011 and September 2015. During the study, 22 patients dropped out (15%). Baseline clinical assessment was part of the clinical care of COPD patients referred to the PR service. DAL was assessed for seven consecutive days prior to the start and following the completion of PR using a validated for COPD patients activity monitor (Actigraph GT3X, Actigraph LLC Pensacola, FL) [9]. Activity monitoring data were analyzed by the ActiLife software version 5.10.10. Prior to the start of the PR programme patients were stratified for

DAL (i.e., >5000 vs <5000 steps/day) [10]. Following stratification patients were randomized in 2:1 ratio into the Interval Training Group (ITG) or the Usual Care Group (UCG) [11]. Medical treatment was not altered throughout the study in either of the groups. Exclusion criteria for participation in PR programme have been described elsewhere [8]. Patients with a minimum of 4 valid days, including only days with at least 8 hours of wearing time during waking hours (as defined between 07:00am-08:00pm) were contained in this analysis [12]. The interval programme included supervised exercise training consisting of cycling exercise 3 days/week for 12 weeks on electromagnetically braked cycle ergometers [7,8]. Patients assigned to ITG, exercised at a mean intensity of 130±18% of baseline peak work rate for 45 min by alternating 30-s exercise intervals with 30-s rest periods. The PR programme included resistance training for upper and lower limbs, breathing retraining, dietary advice and education programme. No specific education session on changes in DAL was included. Data are reported as mean±SD. Normal distribution was assessed using the Shapiro-Wilk test revealing that all data were normally distributed. Baseline characteristics between the two groups were compared using independent paired t-test. Two-way ANOVA with repeated measures were employed to evaluate intervention *x* time interaction effects. Pair-wise differences were identified using Tukey's honestly significant difference *post hoc* procedure.

Baseline characteristics were similar between the two groups (Table 1). Significantly intervention *x* time interaction effects were observed between the ITG and the UCG for aerobic and functional capacities, respiratory symptoms, health related quality of life, emotional status and all physical activity outcomes (Table 1). ITG patients significantly and clinical meaningfully increased the mean number of steps/day (by 1094±1158 steps/day, or 27% from baseline value) and the time spent in lifestyle, light and moderate intensity of daily physical activities following the 12-week high-intensity interval training programme (Table 1). Furthermore, 38 out of 85 patients (45%) exhibited an increase of >1.000 steps/day whilst 6 more patients (7%) demonstrated an increase ranging between 900-1000 steps/day. In addition, ITG patients had an increase over UCG of 1475±1358 steps/day or 36% from baseline value following the 12-week interval training programme.

The present data demonstrate that in patients with COPD high-intensity interval exercise training as part of a comprehensive PR programme can induce clinically meaningful improvements in DAL in

terms of amount and intensity of daily physical activity. The importance of these novel findings is reinforced by the fact that the study was conducted in accordance with the recently published for COPD patients standardized procedure for DAL analysis [12] as well as by the inclusion of a control group [5].

In the present study, the observed clinically meaningful increase in daily number of steps observed in the ITG group was accompanied by improvements in ventilatory, central hemodynamic and peripheral muscle capacities (Table 1). In view of the fact that intensity of the exercise training stimulus is a critical determinant of the magnitude of physiological adaptations that occur in response to training [13], interval training portraits as more favorable for COPD patients who are unable to sustain moderate intensities for long periods of time to achieve substantial physiological effects due to symptom limitations of dyspnea and leg discomfort [4]. Therefore, it is concluded that induction of true physiological adaptations following interval training can be converted to clinically meaningful improvements in DAL in COPD patients.

The content of the PR programme in the present study did not include physical activity counseling interventions. However, it is anticipated that the decrease in respiratory symptoms, the improvement in anxiety and depression emotional status and health related quality of life that was observed following interval rehabilitative exercise training, might have positively impacted on behavioral status and thus have further contributed to achieve meaningful improvements in DAL. However, future studies aiming at investigating the association between physiological and health related outcomes with behavioral status for physical activity are warranted in order to support the abovementioned arguments.

Conventional rehabilitative exercise programmes have fallen short to show significant increases in time spent in moderate activities in patients with COPD [ref]. In this context, a recent study showed that training modalities mimicking everyday-life activities has proven to positively impact on DAL [14]. Interestingly, authors found that following 12 weeks of Nordic walking training, intensity of walking was significantly improved [14]. In our study we found that time spent in lifestyle and moderate activities significantly increased by 9±19 and 7±11 minutes/day, respectively. Thus, based on previous and these findings it can be concluded that interval training, which by some means mimics

the mode that patients with COPD perform everyday-life activities, can better be adapted into patients' activity status compared to conventional constant-load exercise training programmes.

To extent of our current knowledge, this is the first randomized control study demonstrating that high-intensity interval rehabilitative exercise training induces a clinically meaningful increase in DAL in patients with COPD.

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Table 1. Outcomes before and after 12 weeks of high-intensity interval exercise training programme

Variable	Interval Training Group (n=85)	Interval Training Group (n=85)	Usual Care Group (n=43)	Usual Care Group (n=43)
	pre	post	pre	post
Demographics- Anthropometrics data				
Age, *years*	65 ± 8		67 ± 8	
Gender, *male/female*, (*%)*	67/17 (80)		36/7 (84)	
BMI, kg/m^2	27.2 ± 4.7	27.3 ± 4.5	27.8 ± 5.2	27.7 ± 5.3
FFMI, kg/m^2	18.4 ± 2.9	18.6 ± 2.8	18.5 ± 2.61	18.6 ± 2.3
Pulmonary function and disease related data				
FEV_1, *%predicted*	48.8 ± 19.4	48.9 ± 19.1	44.9 ± 19.0	44.5 ± 19.2
FEV_1/FVC,*%*	51.8 ± 15.9	50.9 ± 16.3	48.0 ± 14.1	47.3 ± 13.9
FRC, *%predicted*	159 ± 44	157 ± 43	167 ± 43	163 ± 40
TLC, *%predicted*	119 ± 23	117 ± 22	125 ± 29	124 ± 29
RV/TLC, %	52.6 ± 16.7	51.9 ± 10.4	56.2 ± 15.2	56.8 ± 15.8
TLco, *%predicted*	59.3 ± 21.8	59.6 ± 23.1	55.0 ± 22.8	55.9 ± 23.0
GOLD stages (I/II/IV/V), %	(4/43/31/22)		(5/39/35/21)	
Packs per year	52 ± 20		55 ± 19	
Number of Comorbidities/patient	1.3 ± 1.3		1.4 ± 1.7	
Number of Exacerbations/patient	1.11 ± 1.09		1.21 ± 1.11	
Number of Hospitalizations/patient	0.86 ± 0.73		0.88 ± 0.76	
Exercise variables and performance				
Peak work rate, *watt*	64 ± 29	82 ± 33*	66 ± 26	65 ± 19†
Peak O_2 uptake, *ml/min/100g*	16.4 ± 3.9	17.8 ± 4.0*	15.7 ± 2.9	15.5 ± 4.1†
Peak Minute Ventilation, *L/min*	45.5 ± 7.1	49.6 ± 9.4*	46.1 ± 8.7	45.3 ± 7.9†
Peak Cardiac output, *L/min*	10.7 ± 2.1	12.5 ± 2.3*	10.2 ± 2.8	10.1 ± 2.5†
6MWD, *meters*	387 ± 113	434 ± 121*	379 ± 106	373 ± 100†
Quadriceps muscle force, *kg*	29.7 ± 11.9	33.9 ± 13.2*	30.4 ± 10.9	29.8 ± 11.1†
Quadriceps muscle endurance, *sec*	31.5 ± 17.1	42.6 ± 16.7*	32.6 ± 18.6	33.1 ± 18.1†
Symptoms, Health related quality of life and Emotional status				
mMRC, *scale*	2.26 ± 1.04	1.6 ± 1.07*	2.37 ± 0.92	2.24 ± 0.99†
CAT, *score*	16.0 ± 6.1	12.1 ± 5.3*	16.3 ± 7.0	15.4 ± 8.0†
CCQ, *total score*	1.90 ± 1.0	1.48 ± 1.0*	1.95 ± 0.9	2.00 ± 0.9†
CRDQ, *total score*	86.4 ± 27.1	98.4 ± 21.6*	87.9 ± 23.8	89.1 ± 26.1†
HADS, *total score*	13.6 ± 9.4	10.9 ± 8.0*	13.0 ± 7.9	12.8 ± 8.2†
Daily Activity Levels (DAL)				
Sedentarism, %	69%		68%	
Wearing time (07:00am-08:00pm), *min*	765 ± 39	759 ± 49	755 ± 41	749 ± 40
Daily number of steps	4043 ± 2484	5136 ± 2866*	3871 ± 2526	3453 ± 2493†
Time spent in sedentary activities, *min*	576 ± 87	530 ± 97*	560 ± 82	566 ± 89†
Time spent in light activities, *min*	135 ± 62	160 ± 67*	144 ± 56	137 ± 65†
Time spent in lifestyle activities, *min*	39 ± 24	48 ± 32*	38 ± 26	34 ± 25†
Time spent in moderate activities, *min*	13 ± 15	20 ± 19*	12 ± 19	12 ± 17†

Values are expressed as mean ±SD. * Within-group significant differences. † Between-groups significant differences (interval training group vs usual care group). BMI: body mass index, FFMI: Fat free mass index. FEV_1: forced expiratory volume in one second; FVC, forced vital capacity, FRC: functional residual capacity, RV: residual volume, TLC, total lung capacity, TL_{CO}: diffusing capacity of the lung for carbon monoxide, GOLD: Global Initiative for Obstructive Lung Disease 6MWD: six minute walk distance, mMRC: Modified Medical Research Council questionnaire, CAT: COPD Assessment Test, CCQ: Clinical COPD Questionnaire, CRDQ: Chronic Respiratory Disease Questionnaire, HADS: Hospital Anxiety Depression scale. Lung function was performed following ATS-ERS recommendations. Cardiac output assessed by impedance cardiography [11]. 6MWD measured as the best of 2 six minute walk tests, following ATS-ERS guidelines. Isometric quadriceps muscle force and endurance measured with the patient fixed in 90° hip and knee flexion [15]. Exacerbation history and Hospitalization refer to the last 12 months before enter the study. Sedentarism has been defined as a step count lower than 5000 steps/day [9].