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ELOISA MARIA GATTI REGUEIRO

FUNCTIONAL STATUS AND DYSPNEA AS PERFORMANCE OF ACTIVITIES OF DAILY LIVING AFTER PHYSICAL AND INSPIRATORY MUSCLE TRAINING IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

[1] STUDY I: Physiological performance of patients with COPD during activities of daily living after a physical training with and without inspiratory muscle training: pilot study.

[1] STUDY II: Dyspnea and functional status: responsiveness of measuring instruments on the activities of daily living post different training programs in patients with COPD.

[2] STUDY III: The Minimal Important Difference of the Pulmonary Functional Status and Dyspnea Questionnaire - Modified version in Patients with Chronic Obstructive Pulmonary Disease.

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Tese de Doutorado apresentada ao Programa de Pós-Graduação em Fisioterapia da Universidade Federal de São Carlos, como parte dos requisitos para a obtenção do título de Doutor em Fisioterapia. Área de concentração: Processos de Avaliação e Intervenção em Fisioterapia. Orientador: [1] Profª. Drª. Valéria Amorim Pires Di Lorenzo e [2] Prof. Dr. Thierry Troosters (Doutorado Sanduíche *Katholieke Universiteit Leuven*).

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"Deus nos fez perfeitos e não escolhe os capacitados, capacita os escolhidos. Fazer ou não fazer algo só depende de nossa vontade e perseverança".

(Albert Einstein)

Pois...

"Nada na vida deve ser temido, somente compreendido. Agora é hora de compreender mais para temer menos."

(Marie Curie)

Visto que...

"Quando nada é certo, tudo é possivel."

(Margaret Drabble)

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LIST OF ABBREVIATIONS

ADL	Activities of daily life
BMI	Body mass index
BS	Borg scale
COPD	Chronic Obstructive Pulmonary Disease
CPET	Cardiopulmonary exercise test
CRDQ	Chronic Respiratory Disease Questionnaire
ECG	Electrocardiogram
ERES	Empirical rule effect size
ES	Effect size
FEV_1	Forced expiratory volume in one second
FVC	Forced vital capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GPT	General physical training
GPT+IMT	General physical training + inspiratory muscle training
HR	Heart rate
HRQoL	Health-related quality of life
ICC	Intra-class correlation coefficient
IMT	Inspiratory muscle training
[IQI]	Interquartile interval
LL	Lower limb
LCADL	London Chest Activity of Daily Living
MID	Minimal important difference
MRC	Medical Research Council

PFSDQ-M	Pulmonary Functional Status and Dyspnea Questionnaire – Modified version
PImax	Maximal inspiratory pressure
PR	Pulmonary rehabilitation
RR	Respiratory rate
SD	Standard deviation
SEM	Standard error of measurement
SpO_2	Peripheral oxygen saturation
UL	Upper limbs
VE	Pulmonary ventilation
VE/VO_2ratio	Ventilatory equivalent for oxygen
VO_2	Oxygen consumption
VE/VCO_2ratio	Ventilatory equivalent for carbon dioxide
6MWD	Six-minute walking distance

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CHAPTER 1: GENERAL INTRODUCTION AND RATIONALE

Activities of Daily Living, Dyspnea and Inspiratory Muscle Training in Patients with COPD

Chronic obstructive Pulmonary Disease (COPD) is a disease with high clinical and economic burden. By the year 2030 COPD will be among the top five chronic diseases in terms of global mortality and morbidity (1). The disease is equally present in developing and developed countries. The condition is associated with a substantial utilization of health care resources as a result of hospital admissions and the need for ongoing outpatient care(2) . The low level of spontaneous physical activity reduces the performance of these patients (3) and contributes to the development of skeletal muscle weakness and comorbidity. Patients often experience shortness of breath and a decline in exercise tolerance, resulting in disability in the performance of activities of daily living (ADL).

The kind of daily activities affected are mainly activities such as bathing, carrying things or walking up stairs, which determine a person's ability to move around or the level of care that they may require. For this reason, improving the patient's symptoms, their performance and functional status is an important treatment aim in clinical practice. This goal is achieved by exercise training, which is the component with the strongest level of evidence of a pulmonary rehabilitation program(4). Exercise training improves exercise capacity, quality of life, decrease dyspnea, anxiety or depression, and the frequency and length of hospitalization (5).

However, less is known on the physiological benefits (ventilatory and metabolic responses) during the execution of ADL in these patients (6;7) after a rehabilitation program or exercise training. According to Lahaije et al, pulmonary ventilation ($\dot{V}E$) and oxygen uptake ($\dot{V}O_2$) increase during the performance of simple ADL; however, it is unknown why and when in

the course of the disease physiological limitation begins to have its effects in daily life and/or activity level is reduced(8).

Additionally, several studies (9;10) show the added value of inspiratory muscle training (IMT) in conjunction with general exercise training in patients with COPD to improve the inspiratory muscle strength and endurance and decrease the dyspnea sensation. These data are in accordance with a recent review of Gosselink et al(11). They concluded that IMT is an effective treatment modality in patients with COPD to improve respiratory muscle strength and endurance. Moreover, it reduces dyspnea and improves the functional exercise capacity and health-related quality of life (HRQoL). Their findings evidenced that patients with more advanced muscle weakness seem to be better responders, especially when considering IMT in addition to general exercise training (11). However, there are no studies reporting the potential benefits of IMT on ADL. Furthermore, few studies investigated the metabolic and ventilatory demand of ADL in patients with COPD (6;7) after a rehabilitation program or a physical training, justifying our study.

Instruments to Quantify Dyspnea and Functional Status at COPD

Different instruments exist to quantify the functional performance (change in activity levels) and dyspnea related to ADL. The Borg scale is perceived exertion scale used to measure overall exertion during physical activity (12). It was modified to a form 10 point scale including written indicators of severity to anchor specific numbers on the scale (13). Actually, the scale has been used widely to quantify perceived symptoms such as breathless and muscle fatigue during exercise (14;15). The Medical Research Council (MRC) (16) is a simple scale to quantify functional impairment due to dyspnea. The scale is based on the sensation of breathing difficulty experienced by the patient during ADL and consists of five statements about perceived breathlessness (17). It is a traditionally used instrument in the

international literature, mainly because it is easy to apply and understand. The London Chest Activity of Daily Living (LCADL), which has four domains (personal care, household activities, physical activities, and leisure activities), was developed with the aim of assessing the impairment of ADL in patients with COPD (18). The scale has proven to be a reliable, valid, and sensitive instrument for assessing patients' response to pulmonary rehabilitation programs(18) .In addition, the Pulmonary Functional Status and Dyspnea Questionnaire - Modified version (PFSDQ-M) that quantifies the functional performance (change in activity levels), dyspnea and fatigue related to ADL experienced by patients compared to the period before disease onset in 10 common activities, is also a clinically useful instrument (19).

Although there are studies that evaluate scales and questionnaires related to changes in ADL and dyspnea in patients with COPD, just few reports in literature compare and correlate the results obtained by those with metabolic and ventilatory responses before and after pulmonary rehabilitation program, during the simulation of daily tasks.

The clinical importance of benefits from intervention is the key to truly value their addition in the therapeutic armentarium. In this context, findings of the minimal important difference (MID) of an interested domain, which is defined as "the smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient's management" (20-22), have been extensively studied for functional exercise tests (23-25) and HRQoL (26).

An instrument designed to quantify the functional performance (change in activity levels), dyspnea and fatigue related to ADL is the PFSDQ-M (19). The MID is yet to be determined. Symptoms of fatigue and dyspnea measured with the PFSDQ-M are assessed during ten common activities, such as combing or washing hair and putting on a shirt. The magnitude of change in functional status measurements is difficult to interpret in the absence of the

orientation on what constitutes the MID for this patient reported outcome (27). Methods are available to establish a degree of change that could be considered different as well as clinically meaningful. Currently it is unknown which change in PFSDQ-M score should be considered a clinically relevant change. Approaches to establish the threshold for the PFSDQ-M would obtain the measures of improvement of dyspnea, fatigue and change in ADL and in six minute walk distance (6MWD) with a pulmonary rehabilitation program.

Rationale of the studies

In Chapter 2, the **Study I** of this thesis aims to investigate changes on perception of dyspnea (Borg scale), metabolic and ventilatory responses during a standard set of ADL tasks after a physical training and physical training plus inspiratory muscle training (Conducted in Brazil – UFSCar, São Carlos). Despite, it is already known that exercise training improves exercise capacity, the performance of activities of daily living, decreases dyspnea, and enhances the inspiratory muscle strength in patients with COPD (5;9), less is known on the physiological benefits (ventilatory and metabolic responses) during the execution of daily life activities (ADL) in patients going through physical training with additional or non-additional inspiratory muscle training (IMT). However, it is unknown to what extent pulmonary rehabilitation programs aimed at enhancing also respiratory muscle function, may affect oxygen uptake, ventilation, execution time and symptoms in patients with COPD during the execution of ADL tests.

The objective of the **Study II** of this thesis in Chapter 3, is to evaluate the responsiveness in the perception of dyspnea during the ADL set by Borg scale, the dyspnea self-reported in the MRC, on functional status and dyspnea self-reported in LCADL scale and functional performance (change in activity levels), dyspnea and fatigue, reported in the PFSDQ-M at baseline and after two different training programs; in addition, to verify the effect of

inspiratory muscle training on symptoms (Conducted in Brazil – UFSCar, São Carlos). Patients with COPD often experience shortness of breath and a decline in exercise tolerance, resulting in disability to perform occupational and activities of daily living (ADL). Although there are studies that evaluate scales and questionnaires related to changes in ADL and dyspnea in patients with COPD(28), just few reports in the literature compare the results obtained by those in the simulation of daily tasks before and after a general physical training and physical training associated to IMT(10;29). Hence, our hypothesis is that the performance of ADL, the dyspnea and functional status reported from BS, the LCADL and the PFSDQ-M domain are improved with the IMT combined with general exercise training in patients with COPD.

Chapter 4 provides information regarding the use of specific tools, questionnaires and scales, to quantify dyspnea allow to classify the severity of the symptom and the distress generated thereby, and to monitor it over time, determination of the MID of these tools is important for several reasons, as it facilitates judging the magnitude of the benefit when comparing two treatments, calculating sample sizes, making inferences about the percentages of patients improved by a therapeutic intervention (e.g. the number needed to treat), and making cost effectiveness comparisons (30). Currently it is unknown which change in PFSDQ-M score can be considered as a clinically relevant change. Establishing the threshold of MID for the PFSDQ-M would add to the interpretation of the improvement of dyspnea and fatigue symptoms and change in ADL after a pulmonary rehabilitation (PR) program (31;32). Due to the importance of this field the **Study III** aims to establish the minimal important difference of the PFSDQ-M in patients with COPD (Conduced in Belgium – KU Leuven, Leuven).

The clinical relevance and limitations of this thesis will be explained further in each study.

A summary regarding the main findings of this thesis and future directions is provided in Chapter 5.

Studies

The thesis is divided in three manuscripts. The **Studies I** and **II** will be submitted after committee appreciation. The **Study III** was submitted at the Respiratory Research Journal (MS ID: 8427111858348347). http://respiratory-research.com/

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CHAPTER 2: STUDY I

Physiological performance of patients with COPD during activities of daily living after a physical training with and without inspiratory muscle training: pilot study.

Manuscript in preparation for submission

Abstract

Background: Exercise training improves exercise capacity, the performance of activities of daily living, decreases dyspnea, and enhances the inspiratory muscle strength in patients with COPD. Less is known on ventilatory and metabolic responses ($\dot{V}_E$, $\dot{V}O_2$) during the execution activities of daily life (ADL) in patients going through physical training with additional or non-additional inspiratory muscle training (IMT). **Aim:** This study aims to compare changes on $\dot{V}_E$ and $\dot{V}O_2$ responses, dyspnea, oxygen saturation and ADL time during a standard set of ADL tasks after two different training programs. **Methods:** A set of 5 ADL using a metabolic system (making bed, taking shower, brushing teeth and combing hair, lifting and lowering containers on a shelf above eye level and below the pelvic waist) was performed by 28 patients with COPD before and after the whole protocol. Patients were divided into two groups. One performed aerobic training, lower limbs (LL) resistive exercise and respiratory exercise (GPT) and the other aerobic training, resistive exercise of LL and an additional IMT (GPT+IMT). 13 composing the GPT (age 67.1±7.3yrs, FEV_1 43.0±4.0%pred) and 15 patients composing the GPT+IMT (age 67.4±11.7yrs, FEV_1 51.0±3.0%pred). **Results:** Both groups had a significant reduction ($p<0.05$) of $\dot{V}_E$, $\dot{V}O_2$ and Borg and a significant improvement of SpO_2 during the ADL set within them showing benefits of physical training on performance of ADL. However, adding IMT did not show additional benefits in those variables between groups. There was a significant difference ($p<0.05$) in PImax in both groups and between them. On the other hand, although there are no differences between groups, both of them improved their performance in the cardiopulmonary test and six minute walking distance. **Conclusion:** The pulmonary rehabilitation reduces metabolic cost of common tasks of daily life as both groups improved their performance in the ADL set and, even with IMT, additional benefits were not perceived.

Introduction

Exercise training improves exercise capacity, the performance of activities of daily life (ADL), decreases dyspnea (5;33), which seriously symptom that affects patients' capacity to perform activities of daily life (ADL) (34-37) and enhances the inspiratory muscle strength in patients with chronic pulmonary obstructive disease (COPD) (9;38). Exercise training and physical activity have been shown to have positive effects in patients with COPD. It is known that these patients show satisfactory improvement concerning exercise tolerance and symptoms of dyspnea and fatigue at all stages of the disease. Additionally, patients who have taken part in training are less afraid of exerting themselves and become more physically active in their daily lives (39;40), the quality of life improves and the sense of well-being increases (4). However, less is known on the physiological benefits (metabolic and ventilatory responses) during the execution of ADL in these patients (6;7) after a rehabilitation program or exercise training. According to Lahaije et al pulmonary ventilation ($\dot{V}_E$) and oxygen uptake ($\dot{V}O_2$) increase during the performance of simple ADL(8); however, it is unknown why and when in the course of the disease physiological limitation begins to have its repercussion in daily life and/or activity level is reduced(8). Domestic daily life activities are typically performed at a higher demand of $\dot{V}O_2$ peak in patients compared to healthy controls (6;7;9). This may lead to discomfort during the performance of domestic ADL. Currently, task-related oxygen uptake and symptom perception during simple self-paced domestic ADL have been studied rarely in COPD (6;7;9;41). It has been suggested that the arm position during the execution of ADL, may be an additional burden, changing the respiratory breathing pattern and thoracoabdominal asynchrony during unsupported arm elevation (42-44). Arm elevation may harm the shoulder girdle muscles and the upper torso in their role as accessory respiratory muscle (42;45). This may further rise the respiratory symptoms in these patients. It is unknown to what extent pulmonary rehabilitation programs

aimed at enhancing also respiratory muscle function, may affect oxygen uptake, ventilation, execution time and symptoms in patients with COPD during the execution of ADL tests. In the last few years two protocols have been developed harm to specifically measure ADL as a representative, objective assessment of function in patients with COPD. The Glittre ADL test (46) and the protocol described by Velloso et al (6) are available to test metabolic and ventilatory parameters of patients with COPD during ADL. The latter has been adapted for use in other studies (15;47). This study aimed to compare changes on ventilatory and metabolic responses ($\dot{V}_E$ and $\dot{V}O_2$), Borg symptom scores, peripheral oxygen saturation (SpO_2) and execution time (s) of a standard set of ADL tasks between patients with COPD that performed two different training programs: an aerobic training, resistive exercise of lower limbs and a respiratory exercise program versus aerobic training, resistive exercise of lower limbs and inspiratory muscle training (IMT). We hypothesized that the ventilatory and metabolic responses during the performance of ADL, the dyspnea reported from Borg scale (BS), the SpO_2 and execution time of a standard set of ADL tasks would ameliorate more in patients with COPD that performed the IMT.

Methods

Study design

A prospective, blind, randomized, parallel groups design was used with a group undergoing 48 sessions of aerobic training, resistive exercise of lower limbs (LL) and respiratory exercise (GPT) and a group undergoing 48 session of aerobic training, resistive exercise of LL and an additional inspiratory muscle training (IMT) (GPT+IMT). Patients allocation was did using a computer software with witch a computer-generated list of random numbers was generated (48).

Inclusion and exclusion criteria

Inclusion criteria were clinical diagnosis of COPD confirmed by post-BD spirometry administered by a pulmonologist, in accordance with the GOLD criteria(49), were clinically stable and had no history of infection and no exacerbation of respiratory symptoms or changes in medication for at least two months before the study, absence of severe cardiac disease as shown by electrocardiogram at rest and during the maximal exercise test, absence of other pathologic conditions which could impair the assessment of the ADL set, *e.g.* orthopedic and cerebrovascular diseases, malignancy, arthritis and rheumatism. Patients were excluded when the medication was modified during the study, in cases of exacerbation, uncontrolled arterial hypertension or hypoxemia (peripheral oxygen saturation [SpO2]) below 85% at rest), or for refusal to provide written informed consent.

Subjects

Forty-two consecutive patients (33 men, 9 women; mean ± standard deviation [mean±SD] age, 69±11 years; forced expiratory volume in one second [FEV_1], 43±14% predictive) were initially included in the study and randomly divided into two groups: GPT and GPT+IMT. None of the patients had been engaged in any exercise-training program before participating in the study. All patients had received a diagnosis of COPD ranging from moderate to very severe according to the GOLD (stages II to IV) (49). In general, patients were all retired or on sick leave and were no longer employed. From the 42 patients included in the study, 9 were excluded: 4 did not achieve the inclusion criteria, 3 did not tolerate the test and 2 would not like to participate in the protocol. Of the 33 patients, 18 composed the GPT+IMT group and 15 the GPT; 3 patients from GPT+IMT and 2 from the GPT were excluded because they had been hospitalized for an acute exacerbation during the protocol, composing the final sample 28 patients before and after a 16 week training: 13 patients that composed the GPT group (aerobic training plus exercises of the trunk and upper limbs (UL) and stretching of

large muscle groups of the trunk) (mean ± SD age, 67.1±7.3 years; FEV_1, 43.0±4.0% predictive) and 15 patients that performed the GPT+IMT with POWERBreathe® (mean ± SD age, 67.4± 11.7years; mean FEV_1, 51.0±3.0% predictive) (Figure 1) (Table 1).

The procedures were performed according to the research ethics guidelines of the Declaration of Helsinki (50). The study protocol was approved by the ethics committee of Universidade Federal de São Carlos - UFSCar, Brazil (protocol number 140/2010) (Attachment I). Before the tests, the procedures were described in detail, and written informed consent was obtained from all patients (Attachment II). The patients did not receive any financial remuneration.

Sample size calculation

Using data from our exercise training program and based on the estimated training effect on dyspnea, we determined that a sample size of 40 (20 per group) would yield 80% power (α= 0.05) to detect a between-group difference of 1.0 point at the minimal clinically important difference (MID) (14) on dyspnea in the Borg Scale during the assessment of the ADL set.

Instruments and measures

All patients were submitted to a baseline and after protocol measures. Spirometry was performed using a portable spirometer (Easy One®) according to international standards (51) The results were expressed as the predictive percentage of Brazilian population (52). Maximal inspiratory pressure (PImax) was measured according to the method of Black and Hyatt (53) . The reference values were described by Neder et al (54).

A cardiopulmonary exercise test (CPET) was performed using a portable metabolic system (MedGraphics VO2000 St. Paul MN, USA) to assess $\dot{V}_E$ and $\dot{V}O_2$. The test consisted of symptom-limited graded exercise on a treadmill with patient breathing room air and its objective were to determine the training intensity and possible cardiovascular contraindications of exercise programs using the modified Bruce protocol (55). The patients were submitted to an incremental test according to the standard of the American Thoracic

Society/American College of Chest Physicians statement on cardiopulmonary exercise testing (56). The heart rate (HR) was monitored continuously by a 12-lead ECG. Functional exercise capacity was assessed by the 6MWT according to the American Thoracic Society recommendations (57).

Assessment of Activities of Daily Life task set

In the standard set of ADL tasks using a portable metabolic system (MedGraphics VO_{2000} St. Paul MN, USA) to assess $\dot{V}_E$ and $\dot{V}O_2$, patients were evaluated by simulated ADL of: getting up and making bed, taking shower and washing one's back, brushing teeth and combing hair, lifting and lowering containers on a shelf above eye level and lifting and lowering containers on a shelf below the pelvic waist. No specific amount of time is stipulated; the patient is only instructed to complete the task. The activities were adapted from Velloso et al (6). During the test, Borg symptom scores, SpO_2 and execution time (s) were measured. Moreover, measures of blood pressure, respiratory rate (RR) and HR were measured in the rest (baseline) and in the end of the set, with the purpose of monitoring.

Training Protocol

The protocol consists of 48 sessions of 60 minutes each, three times per week on alternate weekdays in the outpatient clinic of the university. The aerobic training intensity consisted of 70-80% of treadmill speed and inclination reached in the maximal test symptom-limited, beginning from 20min and finishing with 30min. The training progression was periodically adjusted sustaining the HR in 85% of HRmax and Borg score ranging from 4 to 6. The resistive exercise of lower limbs (using free weights) was done with increment according to patients' tolerance, with periodically adjustments. And the respiratory exercise includes a specific exercise program for mobility and biomechanics of the rib cage, such as exercises of the trunk, UL and additional stretching of global muscles. The other group of patients received the same package of aerobic training and resistive exercise of lower limbs and, an

additional inspiratory muscle training program performed using a threshold inspiratory muscle trainer, the POWERbreathe® (GaiamLtd; Southam, Warwickshire, UK). This equipment was used due to the load amplitude it can generate: from 10 to 90cmH_2O (green – Wellness model), increasing loads from 10 to 10cmH_2O. During the protocol patients received IMT in 7 cycles of 2 minutes of resistive breathing each, followed by 1 minute of rest. They started breathing at a resistance that required generation of 15% of PImax for one week. The load was then increased incrementally 10% each session, to reach generation of 60% of the initial PImax at the end of the first month. IMT was then continued at 60% of the PImax adjusted every two weeks to the new PImax, achieved throughout the next 12-week course of the study (10;29). When oxygen saturation decreased below 90%, the intensity or the duration of the training was reduced. Pursed-lip breathing was used during training to maintain the saturation. For hypoxemic patients and those who desaturate during training (SpO_2<88%), oxygen supplementation was provided (58).

Statistical Analysis

Statistical analyses were performed with SPSS Statistics Release 17.0.0 statistical package. Normal distribution was checked with the Kolmogorov-Smirnov test. The results were described as the mean ± SD, except for Borg symptoms scores, which was shown as the median [interquartile range] due to the non-normal distribution of the data. Comparison of the outcomes in the two assessment moments (*e.g.* at baseline and 4 months of GPT and GPT+IMT programs) was performed. Paired Student *t* test was used to determine differences within groups with the equivalent nonparametric test Wilcoxon due the non-normal distribution if necessary. Between groups analysis ANOVA one-way was used, except for the Borg symptoms scores, which was analyzed with the equivalent nonparametric test Kruskal-Wallis. The level of significance was set at $p<0.05$ for all of the analyses.

Results

The general characteristics of the 28 patients that completed the study are reported in Table 1. There were no statistically significant differences at baseline between the group GPT (n=13) and the group GPT+IMT (n=15). The patients understood the standardized instructions well. There were no adverse events during the ADL set Figure 1 provides the CONSORT chart of patients recruited up to those finishing the study.

Table 2 shows baseline and values after training for the ADL set for each group. While there were no significant changes in executing time in the majority of the ADL, there was statistically significant decrease ($p<0.05$) in values of $\dot{V}_E$, $\dot{V}O_2$, sensation of dyspnea (Borg) and ADL time (ADL making bed) and a significant improvement of SpO_2 within groups. Additionally, change values of these variables after 4 month programs are shown in Table 2. There was no difference between groups after post training in the $\dot{V}_E$, $\dot{V}O_2$, SpO_2, sensation of dyspnea and ADL time values.

Regarding to the ventilatory efficiency, ventilatory equivalents for oxygen ($\dot{V}_E/\dot{V}O_2$ ratio) and carbon dioxide ($\dot{V}_E/\dot{V}CO_2$ ratio) no difference was found both, between and within groups in the ADL set before and post training programs.

Table 3 shows that the PImax (cmH_2O) had a statistically significant rise ($p<0.001$) in GPT and GPT+IMT groups after training and between them. Regarding to CPET a significant fall ($p<0.001$) in the values of $\dot{V}_E$, $\dot{V}O_2$ at isovelocity and inclination were verified. There was no difference between them. Additionally, the 6MWD (m) had a statistically significant increase ($p<0.001$) in both groups with no difference between them (Table 3).

Discussion

The main findings of the present study are that the ventilatory parameters and dyspnea

reduced in both groups after training to perform the ADL set and that the GPT+IMT group shows higher improvement in the PImax than GPT group.

Since patients with COPD are limited in their activities, it is essential to apply simple and easy criteria in clinical practice. Thus, instruments that work with specific dimensions, such as the ADL, have proven to be useful in evaluating limitations in functional activities due to the deterioration of the disease. The application of this type of evaluation in pulmonary rehabilitation and physical training programs provides additional information on functional limitations and in the achievements on therapeutic strategies addressed to the program, such as specified physical training, mainly in patients with limitation to daily activities (59).

The present study demonstrated that the $\dot{V}_E$, $\dot{V}O_2$ and dyspnea improved, showing fall levels in both groups after training and a rise of SpO_2 levels. It is an important result as it is known that simple arm elevation (involved in many ADL) resulted in significant increase in metabolic and ventilatory requirements (6;7). However, as the result of both physical trainings, it improved. Hence the previously reported high levels of oxygen uptake and ventilation in patients with COPD during performance of ADL (8), confirmed in the present study can be reversed with exercise training. In line with observations in other studies (60;61), the addition of IMT did not show additional benefits in those variables when both groups were comparable. Both groups decreased in the values of $\dot{V}_E$ and $\dot{V}O_2$.

It is clear in the literature that the respiratory muscle training may yield improvements in exercise performance in patients with COPD (11;62), and apparently IMT is more correlate with functional benefits such as exercise capacity, 6MWD and inspiratory muscle strength, which were also found in this study, and endurance, dyspnea and improvements in quality of life (9) than improvements in the $\dot{V}_E$ and $\dot{V}O_2$. Similar results were found by Sanchez et al which, did not find significant difference in $\dot{V}_E$, $\dot{V}O_2$ values in the maximal exercise test in patients with COPD that performed and did not perform the IMT (63).

While both rehabilitation programs seemed to result in clinically meaningful improvements in functional exercise tolerance (25) and dyspnea (14;32), the present study did not confirm the additional benefits of IMT on any of the selected outcome variables (physiological or patient report). In addition, also the group, not receiving IMT did enhance PImax. As there is no pure control group we can only speculate the nature of this improvement. Perhaps the respiratory muscle stretch exercises, which were introduced instead of the IMT may also impact on outcome, as these were also reported to decrease chest wall stiffness, particularly in the chest wall respiratory muscles. In addition, there might be an immediate effect of reducing dyspnea at rest (64) and in the respiratory weakness also observed in our study. These findings may also contribute to the fall of physiological variables during the ADL test as it was already quoted that simple arm elevation involved in many ADL resulted in significant increases in metabolic and ventilatory requirements (6;7)

Clinically relevant reduction in symptoms such as dyspnea and fatigue were also found(65); although there is no difference between GPT and GPT+IMT, such as in other studies (60;61). A change in the dyspnea after training of 1 point has been suggested as being the MID. Therefore the mean reduction of 2 points in the present study is likely indicative of clinical importance (14).

Another important outcome of the present study is the enhanced oxygen saturation during ADL activity. Oxygen saturation improved in both groups, with no additional improvement by adding IMT.

Clinical relevance

The study provides data to judge impact of the addition of IMT to conventional exercise training on metabolic load of different ADL.

Limitations of the study

Limitations in the study should be considered. As a preliminary result, the sample size of 40 (20 per group) would yield 80% power (α= 0.05) to detect a between-group difference based on 1.0 point in Borg Dyspnea rating (14) sample size was not met as we were unable to recruit sufficient number of patients to complete the program on time, *e.g.* due to absence, adherence and time without any physical training of patients. Nevertheless, with the present data as pilot, we calculated that 40 patients would be required to find statistically significant differences between both groups. Altogether the benefits of IMT especially at ADL seem small and the clinical relevance can be debated. Eventually, no true control group was evaluated, so it is difficult to put the interesting reductions in pulmonary ventilation and oxygen consumption with ADL activities into perspective. These data therefore should be interpreted with caution. Nevertheless the data suggest that benefits of exercise training programs may reflect the relief of the symptoms in daily life through an improvement in mechanical efficiency and reductions in pulmonary ventilation when carrying out ADL tasks. Proper randomized and controlled studies are needed to further investigate the magnitude of this effect.

Conclusion

These preliminary results suggest that the assessed protocol trainings reduce metabolic cost of common tasks of daily life. The addition of IMT showed higher improvement of PImax when compared to a conventional training. However, it did not result in further benefits in activities of daily life.

Clinicaltrials.gov number NCT01510041

Figures

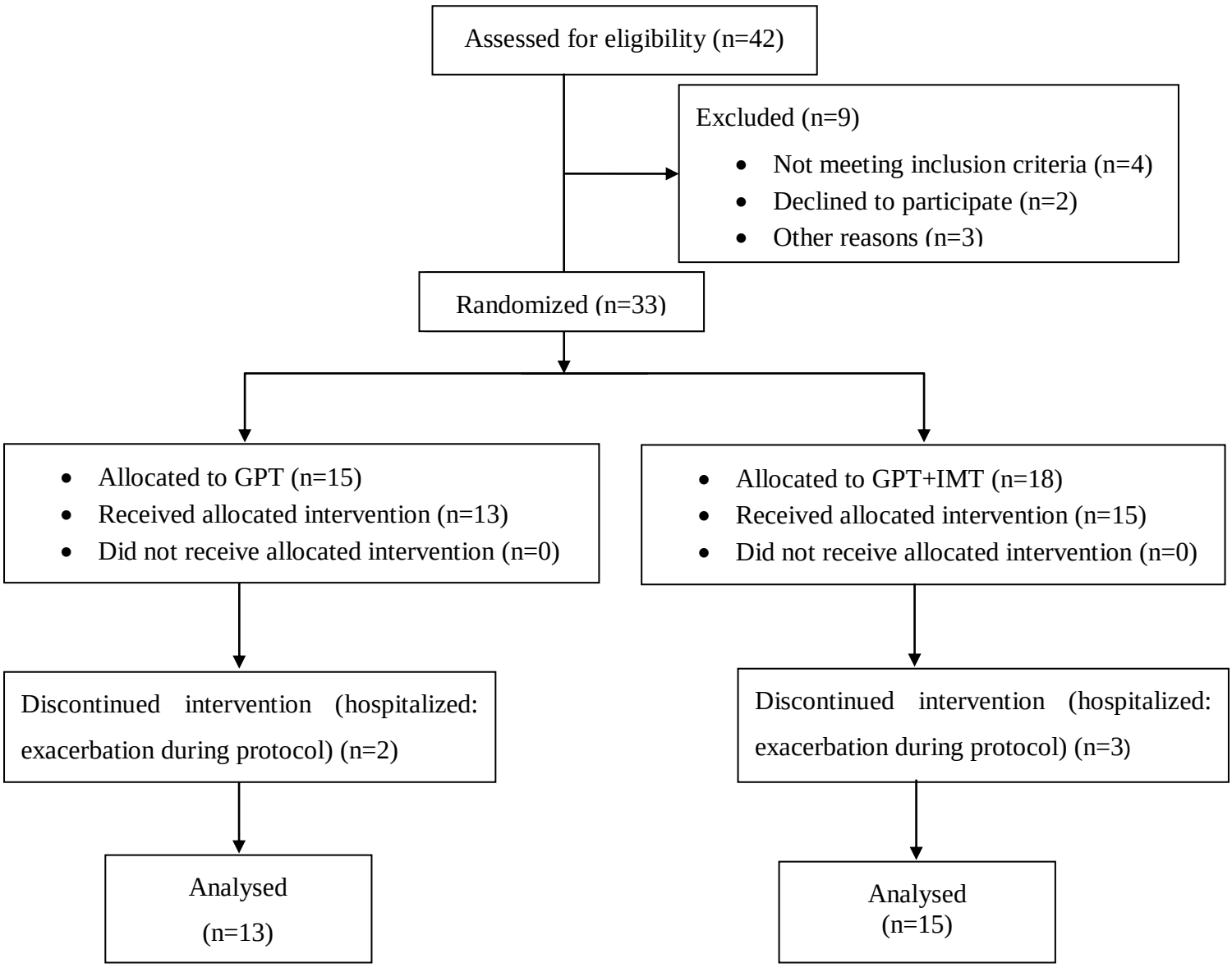

Figure 1. Study design and allocation of subjects.

Tables

Table 1. Baseline characteristics of both groups: General Physical training and General physical training associated with inspiratory muscle training.

Variables	GPT Mean ± SD or median [IQI] n=13	GPT+IMT Mean ± SD or median [IQI] n=15
Gender (male/female)	11/2	14/1
Age (yrs)	67.1±7.3	67.4± 11.7
BMI (kg/m^2)	23.7±3.2	22.2± 3.1
FEV_1 (% pred)	43.0±4.0	51.0± 3.0
FVC (% pred)	66.4±13.9	70.8±17.2
PImax (cmH_2O)	57.0±15.0	50.6±20.5
MRC	1[1-2]	2[1-2]
Time ADL set (s)	2292.9±475.2	2395.6±551.6
CPET speed (Km/h)	3.1±1.0	3.0±0.7
CPET inclination (%)	10.0±3.0	10.0±5.0
CPET VO_2 peak (ml/Kg/min)	16.8±4.2	18.7±4.2
CEPT VE peak (L/min)	28.2±6.4	26.3±3.6
6MWD (m)	478.3±26.1	435.3±89.2

GPT= General physical training; GPT+IMT= General Physical Training plus Inspiratory muscle training; SD = standard deviation; [IQI] = interquartile interval; BMI= body mass index; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; PImax= maximum inspiratory pressure; MRC= Medical Research Council scale; CPET= cardiopulmonary exercise testing; VO_2= oxygen consumption; VE = pulmonary ventilation; 6MWD = six minute walking distance.

Table 2. Baseline, 4-month training values and change values of both groups: General Physical training and General physical training associated with inspiratory muscle training.

	GPT Mean ± SD or median [IQI] n=13			GPT+IMT Mean ± SD or median [IQI] n=15		
Activities and Variables	**Pre**	**Post**	**Delta**	**Pre**	**Post**	**Delta**
Making bed						
V_E (L/min)	28.0±5.0	18.5±2.8*	-9.5±2	31.0±5.5	17.9 ±3.8*	-13±2
VO_2 (ml/Kg/min)	20.1±5.1	12.1±6.5*	-8±7	18.5±3.9	13.2 ±4.1*	-6±4
Borg median [IQI]	2[1 – 2]	0[0 – 1]*	-2±1	2 [1 – 3]	0 [0 – 1]*	-2±1
SpO_2 (%)	90.2±2.6	93.5±3.6*	+3±2	91.5±1.5	93.0 ±1.0	+2±1
Time (s)	236.0±75.7	167.1 ±37.1*	-69±38	233.6±88.0	219.0 ±51.0	-14±36
Taking shower						
V_E (L/min)	28.4±5.8	20.0 ±2.6*	-8±3	31.7±4.9	20.4 ±3.3*	-11±2
VO_2 (ml/min/Kg)	23.3±4.7	14.9 ±5.7*	-8±2	20.3±3.9	15.7±5.4*	-5±2
Borg median [IQI]	3[1 – 3]	1[0 – 1]*	-2±1	3 [2 – 4]	1 [0 – 2]*	-2±1
SpO_2 (%)	90.3±2.5	92.8±2.6*	+3±1	91.2±2.0	93.5±2.0*	+3±2
Time (s)	346.0±64.6	309.6±84.8	-36±20	379.5±102.2	357.4 ±74.3	-22±28
Brushing teeth and combing hair	30.0±4.1	20.2 ±2.0*	-10±2	30.0±5.1	20.3 ±3.1*	-10±2
V_E (L/min)						
VO_2 (ml/min/Kg)	23.8±7.0	15.6±5.0*	-8±2	20.7±3.6	16.7±6.3*	-5±3
Borg median [IQI]	2[1 – 3]	1[0 – 1]*	-1±2	3 [2 – 4]	1 [0 – 1]*	-2±1
SpO_2 (%)	88.3±6.5	91.5 ±4.0*	+3±2	90.0±3.0	92.5 ±2.2	+2±4
Time (s)	470.7±99.7	412.8 ±120.1	-58±20	478.0±84.7	442.0±37.3	-36±47
Lifting and lowering containers on a shelf above eye level	29.8±4.6	20.4 ±3.1*	-10±2	32.0±5.6	20.5 ±3.7*	-11±2
V_E (L/min)						
VO_2 (ml/min/Kg)	21.8±5.5	15.1±4.6*	-7±1	20.1±4.0	15.0±7.0*	-5±3
Borg median [IQI]	3[1 – 3]	1[0 – 2]*	-2±1	3 [2 – 4]	1 [0 – 1]*	-2±1
SpO_2 (%)	89.0±4.7	94.0 ±3.6*	+5±1	89.0±3.0	93.0±2.0*	+4±1
Time (s)	589.0±109.4	549.0 ±136.5	-40±27	623.3±135.7	557.7 ±90.0	-66±46
Lifting and lowering containers on a shelf below the pelvic waist						
V_E (L/min)	29.4±4.2	19.4 ±3.1*	-10±1	31.0±4.8	20.4 ±3.1*	-10±2
VO_2 (ml/min/Kg)	23.0±5.7	16.4±5.1*	-5±1	20.0±4.3	16.1±5.0*	-4±1
Borg median [IQI]	3[1 – 3]	1[0 –1.5]*	-2±1	4 [2 – 4]	1 [0 – 1]*	-3±1
SpO_2 (%)	89.2±5.0	94.0 ±2.7*	+5±2	91.1±2.8	94.0 ±2.2*	+3±1
Time (s)	651.1±125.7	612.3 ±135.4	-40±10	681.0±140.8	610.0±100.5	-71±40

* Pared t test. $p<0.001$. GPT= General physical training; GPT+IMT= General Physical Training plus Inspiratory muscle training; SD= Standard deviation; median [IQI] = median [interquartile interval]; V_E = pulmonary ventilation; VO_2= oxygen consumption; SpO_2= peripheral oxygen saturation.

Table 3. Comparison analyses of baseline and a 4-month training between and within groups (General Physical training and General physical training associated with inspiratory muscle training) at different assessments: maximal inspiratory pressure, cardiopulmonary test and six minute walking test.

Variables	GPT Pre Mean ± SD	GPT Post Mean ± SD	GPT+IMT Pre Mean ± SD	GPT+IMT Post Mean ± SD
PImax (cmH_2O)	57.0±15.0	75.3±9.6 *	50.6±20.5	82.6±22.5*‡
CPET speed max stage (Km/h)	3.1±1.0	4.5±1.0*	3.0±0.7	4.8±1.0*
CPET Inclination (%)	10.0±3.0	12.0±1.5*	10.0±5.0	12.0±2.5*
CPET VO_2 isovelocity and inclination (ml/min/Kg)	16.8±4.2	10.8±3.5*	18.7±4.2	14.8±4.6*
CPET VE isovelocity and inclination (L/min)	28.2±6.4	18.5±5.9*	26.3±3.6	21.2±4.2*
6MWD (m)	478.3±26.1	519.1±70.4*	435.3±89.2	488.4±75.9*

* Pared t test, ‡ ANOVA One Way test, $p<0.001$. GPT= General physical training; GPT+IMT= General Physical Training plus Inspiratory muscle training; SD = standard deviation; PImax= maximum inspiratory pressure; VO_2= oxygen consumption; VE = pulmonary ventilation; CPET= cardiopulmonary exercise testing; 6MWD = six minute walking distance.

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CHAPTER 3: STUDY II

Dyspnea and functional status: responsiveness of measuring instruments on the activities of daily living post different training programs in patients with COPD.

Manuscript in preparation for submission

Abstract

Background: Patients with COPD experience shortness of breath and a decline in exercise tolerance resulting in disability in the performance of activities of daily living (ADL). Physical training and inspiratory muscle training (IMT) improves exercise capacity, functional status and decrease dyspnea**. Aims:** To evaluate the responsiveness of dyspnea during the ADL set by Borg scale, dyspnea self-reported in the Medical Research Council scale (MRC), dyspnea and functional status self-reported in London Chest Activity of Daily Living scale (LCADL) and functional performance, dyspnea and fatigue in the Pulmonary Function Status and Dyspnea Questionnaire - Modified version (PFSDQ-M) at baseline and after a general physical training (GPT) and a GPT+ IMT; additionally, to verify the effect of IMT on symptoms. **Methods:** 28 patients with COPD were enrolled into two groups: 13 at GPT (mean ± SD age, 67.1±7.3 years; FEV_1, 43.0±4.0% predictive) and 15 at GPT + IMT (mean ± SD age, 67.4± 11.7 years; mean FEV_1, 51.0±3.0% predictive). The ADL set, the outcome measures and the reported scales and questionnaire (Borg Scale-CR10 [BS], Medical Research Council [MRC], London Chest Activity of Daily Living [LCADL] and the Pulmonary Functional Status and Dyspnea Questionnaire - Modified version [PFSDQ-M]) were assessed at baseline and after 48 sessions. **Results:** There was a significant ($p<0.01$) fall of dyspnea, evaluated by scales and questionnaires within groups and in the functional status/performance reported in the LCADL and PSFDQ-M. Between groups there was a significant difference ($p<0.05$) regarding to PFSDQ-M in activity and dyspnea domain. PImax improved significantly in both groups and between them ($p<0.05$). **Conclusion:** The measuring instruments assessed were able to detect changes in dyspnea and functional status in both groups. Furthermore, the GPT+IMT group showed higher responsiveness of dyspnea in all assessed instruments.

Introduction

Patients with Chronic Pulmonary Obstructive Disease (COPD) often experience shortness of breath and a decline in exercise tolerance, resulting in disability to perform occupational and activities of daily living (ADL). Dyspnea and fatigue are the common symptoms while performing these activities and the disease progression can limit patients' ability to perform autonomously these domestic tasks (28). The kind of daily activities affected were mainly activities such as bathing, carrying things or walking up stairs, which determine a person's ability to move around or the level of care that he/she may require.

Improving the patient's symptoms, their performance and functional status are important treatment goals in clinical practice. Physical training improves exercise capacity, quality of life, decreases dyspnea and fatigue (5). Additionally, several studies (9;10) show the added value of inspiratory muscle training (IMT) in conjunction with general exercise training in patients with COPD to improve the inspiratory muscle strength and endurance, which consequently improves dyspnea symptoms. However, it is not clearly established in the scientific literature.

There are different instruments to measure the symptoms and to assess the functional performance, dyspnea and fatigue related to ADL. The use of specific tools, questionnaires and scales, to quantify dyspnea allow to classify the severity of the symptom and the distress generated thereby, and to monitor it over time (28). Moreover, these instruments are widely used to evaluate the change in the perception of symptoms post pulmonary rehabilitation and physical training. Dyspnea reduction is one of the most important aims to be achieved in the COPD therapy.

The Borg Scale-CR10 (BS) has been used widely to quantify perceived symptoms such as breathless and muscle fatigue during exercise (14). The Medical Research Council (MRC) is a simple scale to quantify functional impairment due to dyspnea (16). The London Chest

Activity of Daily Living (LCADL), which has four domains (personal care, household activities, physical activities, and leisure activities), was developed with the aim of assessing the impairment of ADL in patients with COPD (18). Additionally, the Pulmonary Functional Status and Dyspnea Questionnaire - Modified version (PFSDQ-M), which quantifies the functional performance (change in activity levels), dyspnea and fatigue (19) related to ADL, is also a clinically useful instrument.

Although there are studies that evaluate scales and questionnaires related to changes in ADL and dyspnea in patients with COPD, just few reports in the literature compare the results obtained by those in the simulation of daily tasks before and after a general physical training and physical training associated to IMT.

The hypothesis is that the performance of ADL, the dyspnea and functional status reported from BS, the LCADL and the PFSDQ-M domain are improved with the IMT combined with general exercise training in patients with COPD.

In this context, the aim of this study was to evaluate the responsiveness in the perception of dyspnea during the ADL set by BS, the dyspnea self-reported in the MRC, on functional status and dyspnea self-reported in LCADL scale and functional performance (change in activity levels), dyspnea and fatigue, reported in the PFSDQ-M at baseline and after two different training programs, and additionally, to verify the effects of IMT on symptoms.

Materials and Methods

Design

A prospective, blind, randomized, parallel group design was used with a group that performed aerobic training, resistive exercise of lower limbs (LL) and respiratory exercises (GPT), and another group with aerobic training, resistive exercise of LL and an additional IMT (GPT+IMT). Outcome measures were assessed at baseline and at the end of the

protocol (after 48 sessions). Patients allocation was done using a computer software with a generated list of random numbers (48).

Inclusion and exclusion criteria

Inclusion criteria were clinical diagnosis of COPD confirmed by post-BD spirometry administered by a pulmonologist, in accordance with the GOLD criteria (49), were clinically stable and had no history of infection and no exacerbation of respiratory symptoms or changes in medication for at least two months before the study, absence of severe cardiac disease as shown by electrocardiogram at rest and during the maximal exercise test, absence of other pathologic conditions that could impair the assessment of the ADL set, e.g., orthopedic and cerebrovascular diseases, malignancy, arthritis and rheumatism; and, cognitive impairment, which compromised the report scales and questionnaire answers. Patients were excluded when the medication was modified during the study, in cases of exacerbation, uncontrolled arterial hypertension or hypoxemia (peripheral oxygen saturation [SpO2]) below 85% at rest), or for refusal to provide written informed consent.

The study protocol was approved by the ethics committee of Universidade Federal de São Carlos - UFSCar, Brazil (protocol number 140/2010) (Attachment I). Written informed consent was obtained from all patients (Attachment II).

Subjects

Forty-two consecutive patients (33 men, 9 women; mean ± standard deviation [mean±SD] age, 69±11 years; forced expiratory volume in 1 second [FEV_1], 43±14% predictive) were initially included in the study and randomly divided into two groups: GPT and GPT+IMT. They were compared before and after protocols through perception of dyspnea with BS during the ADL set, perception of dyspnea self-reported in the MRC, functional status and dyspnea self-reported in LCADL and the interviewed version of the PFSDQ-M. All patients had received a diagnosis of COPD ranging from moderate to very severe, according to

GOLD (stages II to IV) (49) . From the 42 patients included in the study, 9 were excluded: 4 did not achieve the inclusion criteria, 3 did not tolerate the test and 2 would not like to participate in the protocol. Of the 33 patients, 18 composed the GPT+IMT group and 15 the GPT; 3 patients from GPT+IMT and 2 from the GPT were excluded because they had been hospitalized for an acute exacerbation during the protocol. The final sample consisted of 28 patients before and after a 16 week training: 13 patients taking part of the GPT group (aerobic training plus exercises of the trunk and upper limbs and stretching of large muscle groups of the trunk) (mean ± SD age, 67.1±7.3 years; FEV_1, 43.0±4.0% predictive) and 15 patients that performed the GPT+IMT with PowerBreathe® (mean ± SD age, 67.4± 11.7 years; mean FEV_1, 51.0±3.0% predictive). None of the patients had been engaged in any exercise-training program before participating of this study.

Sample size calculation

Using data from our exercise training program and based on the estimated training effect on dyspnea, we determined that a sample size of 40 (20 per group) would yield 80% power (α= 0.05) to detect a between-group difference of 1.0 point at the minimal clinically important difference (MID) (14) on dyspnea in the BS during the assessment of the ADL set.

Instruments and measures

All patients were submitted to a baseline and after protocol measures. Spirometry was performed using a portable spirometer (Easy One®) according to international standards (51) The results were expressed as the predictive percentage of Brazilian population(52). Maximal inspiratory pressure (PImax) was measured according to the method of Black and Hyatt (53). The reference values were described by Neder et al (54). A cardiopulmonary exercise test (CPET) was performed using the modified Bruce protocol (55). The patients were submitted to an incremental test according to the standard of the American Thoracic Society/American College of Chest Physicians statement on cardiopulmonary exercise testing (56). The heart

rate (HR) was monitored continuously by a 12-lead ECG. Functional exercise capacity was assessed by the 6MWT according to the American Thoracic Society recommendations (57).

Assessment of the Borg Scale

The original perceived exertion scale described by Borg comprised a scale from 6 to 20 used to measure overall exertion during physical activity (12). It was modified to a form 10 point scale including written indicators of severity to anchor specific numbers on the scale (13). Actually, the scale has been widely used to quantify perceived symptoms such as breathless and muscle fatigue during exercise (14;15).

Assessment of Medical Research Council

The MRC is a clinical dyspnea scale based on the sensation of breathing difficulty experienced by the patient during ADL (66); which rates the type and magnitude of dyspnea according to five grades of increasing severity . The values 3, 4, or 5 correspond to moderate to severely disabling COPD and grades 1 and 2 are classified as mild COPD (17).

Assessment of the London Chest Activity of Daily Living

The LCADL contains 15 ADL items divided into four domains (personal care, household activities, physical activities, and leisure activities) (18;67) with the aim of assessing the impairment of ADL in patients with COPD. The patients evaluated the degree of dyspnea that interferes with these ADL, assigning a number from 0-5 to each activity. A sub-total is calculated for each component and a total score formed by the sum of the four component sub-totals, with high numbers indicating a greater limitation to ADL (68).

Assessment of Pulmonary Functional Status and Dyspnea Questionnaire – Modified version

The PFSDQ-M consists of three components: dyspnea, fatigue and change in activities experienced by patients compared to the period before disease onset in 10 common activities (19). For each component, each activity is scored on an 11 point scale ranging from 0 to 10.

Ratings on the dyspnea and fatigue component range from 0 “No shortness of breath/fatigue” to 10 “Very severe shortness of breath/fatigue” performing the specific activities; and, ratings on the change in activities range from 0 “As active as I’ve ever been” to 10, “Have omitted entirely (the activity)”. For each of the three components a score ranging from 0 to 100 is calculated with lower scores indicating a better functional status (16). The five general survey questions in the dyspnea and fatigue components are considered informative and qualitative and these answers are not further analyzed.

Assessment of Activities of Daily Life task set

In the standard set of ADL tasks using a portable metabolic system (MedGraphics VO_{2000} St. Paul MN, USA) to assess ventilatory and metabolic parameters ($\dot{V}_E$ and $\dot{V}O_2$) patients were assessed by simulated ADL of: getting up and making bed, taking shower and washing one’s back, brushing teeth and combing hair, lifting and lowering containers on a shelf above eye level and lifting and lowering containers on a shelf below the pelvic waist. No specific amount of time was stipulated; the patient was only told to complete the task. The activities were adapted from Velloso (6). During the test, Borg symptom scores, SpO_2 and execution time (s) were measured. Moreover, measures of blood pressure, respiratory rate (RR) and HR were measured in the rest (baseline) and in the end of the set, with the purpose of monitoring.

Training Protocol

The protocol consists of 48 sessions of 60 minutes each, three times per week on alternate weekdays in the outpatient clinic of the university. The aerobic training intensity consisted of 70-80% of treadmill speed and inclination reached the maximal test symptom-limited, beginning from 20min and finishing with 30min. The training progression was periodically adjusted sustaining the HR in 85% of HRmax and Borg score ranging from 4 to 6. The resistive exercise of lower limbs (using free weights) was performed with increment according to patients’ tolerance, and with periodically adjustments. And the respiratory

exercise includes a specific training program for mobility and biomechanics of the rib cage, such as exercises of the torso, upper limbs and additional stretching of global muscles. The other group of patients received the same package of aerobic training, resistive exercise of lower limbs and also received an additional inspiratory muscle training program performed with the POWERbreathe® (GaiamLtd; Southam, Warwickshire, UK). This equipment was used due to the load amplitude it can generate: from 10 to 90cmH_2O (green – Wellness model), increasing loads from 10 to 10cmH_2O. Patients received IMT in 7 cycles of 2 minutes of resistive breathing each, followed by one minute of rest. Inspiratory load was set at minimally 15% of PImax in the first week, increasing 10% each session to reach 60% of the initial PImax at the end of the first month. From the second to the fourth month the training loads were adjusted every two weeks to maintain 60% of the actual PImax throughout the 16-week course of the study (10;29).

Statistical Analysis

Statistical analysis was performed with SPSS Statistics Release 17.0.0 statistical package. As we were analyzing ordinal data non-parametric statistical tests were used. The results were described as the median [interquartile range]. Characteristics of the sample were described as mean ± SD due to the normal distribution of these data. Comparison of the outcomes in the two assessment moments (*e.g.* at baseline and 4 months of GPT and GPT+IMT programs) was performed. Wilcoxon test was used to determine differences within groups with the equivalent parametric pared Student *t* test due to the normal distribution. Between groups Kruskal-Wallis test was used, with the equivalent parametric ANOVA one-way. The level of significance was set at $p<0.05$ for all the analysis.

Results

The general characteristics of the 28 patients that completed the study are reported in Table 1. There were no statistically significant differences at baseline between the group GPT (n=13) and the group GPT+IMT (n=15).

Table 2 shows baseline, post-test values and change after both programs for MRC, LCADL, PFSDQ-M, BS scores and PImax of both groups.

Within groups, after both program there was a significant ($p<0.01$) fall of dyspnea sensation evaluated to different questionnaire and scales (Table 2). In addition, there was an improvement in the functional status/performance in both groups after training reported in the LCADL and PSFDQ-M. Although, there was no significant improvement in fatigue domain, which is in accordance with patients performance during the ADL set, as both groups generally did not report fatigue during the proposed ADL assessment.

Between groups there was a significant difference ($p<0.05$) before and after tests only in the PFSDQ-M in activity and dyspnea domain, with higher decrease in the GPT+IMT group. There was no difference in fatigue domain. Moreover, there was no significant difference between groups related to dyspnea symptom reported in MRC, LCADL and during the ADL set reported by the BS (Table 2).

Regarding to PImax there was an improvement in both groups. It was found a statistically significant rise ($p<0.05$) in GPT and GPT+IMT groups after training and between them (Table 2).

Discussion

Patients with COPD typically experience symptoms of dyspnea and fatigue when performing ADL. Consequently, improving the patient's functional status and dyspnea symptom during ADL is an important achievement for treatment (69;70). This goal is accomplished by

exercise training, as it is reported by different scales and questionnaires that quantify the dyspnea sensation, the experienced change in performing ADL compared with the period before disease onset and fatigue symptom which are related to ADL (71).

In our study both training groups showed significant improvement in the BS during the ADL set after both training programs. In the MRC the result improvements were observed only in the GPT+IMT group. Regarding the LCADL, its results were noticed in self-care, domestic, physical, leisure domains and in total score. In the PFSDQ-M there was an improvement in change in activities and dyspnea domains. These results are in accordance with other studies as an effect of physical training (69;72).

The dyspnea's fall in the BS score in the ADL assessment suggests an improvement in the ability to perform autonomous personal and domestic tasks. Nevertheless, between groups, the GPT+IMT shows additional benefit in the minority of exposed situation on symptoms such as PFSDQ-M in activity and dyspnea domain, with higher decreases in this group.

The clinical consequence of the changes obtained in the dyspnea after training can be evaluated by the MID(65) , that is 1 point in the BS and has showed a clinically important improvement in this symptom (14), which is in accordance with our results. The MID is defined as the smallest difference in score in the domain of interest perceived as beneficial, with the absence of troublesome side effects, without excessive efforts, changing the patient's self-management (20-22). An improvement on dyspnea was also found in the MRC score in GPT+IMT group, which is in accordance to previous studies that support data that the IMT decreases the dyspnea sensation (9). The improvement reported in the MRC corroborate results about the known MID of MRC, which is a variation of 1 point in the scale, showing a clinical improvement (73). This data is in line with our results, even though our patients are, in their majority, classified with MRC grade 2 and GOLD II and III in both groups and did not show significant difference after GPT. Wedzicha et al suggest that

patients with moderate dyspnea (MRC grade 3 and 4), who were regularly taken out of the house, showed quite large improvements in exercise capacity after physical training and patients with severe disability (MRC grade 5), who were largely housebound owing to dyspnea, showed no improvements in exercise performance following individualized (74). In contrast, Evans et al showed that the benefits are equal in patients with lower or higher MRC score (75). However, it might be considered that it is already known that the MRC scale may not be specific enough to detect moderate changes due to the limited number of present levels (28) and is addressing only a small number of specific domestic ADLs (e.g. walking and dressing or undressing) (15).

Regarding to LCADL, previous studies showed that this scale evaluates patient ability to perform ADL (18;67;76) and is a reliable tool for evaluating dyspnea during these ADL (18;67). The Brazilian validated version (68) used in our study showed less impairment in ADL reported by patients of both groups, even if there was no training based on the ADL protocol set. It is suggested that the effects of pulmonary rehabilitation (PR), which include physical training, improve exercise tolerance, reduce symptoms and HRQoL (4). The degree of dyspnea that interferes with the ADL assessed in the scale fell in the total score and each domain, even the MID of the LCADL is already unknown to support our results. Moreover, previous studies already showed significant improvement in the LCADL after training in patient with COPD (72).

Regarding the PFSDQ-M our results show a significant improvement in the change in activity, dyspnea and fatigue domains within groups and between them, and in change in activity and dyspnea domains, supporting an additional effect of IMT on symptoms and functional status (9); even that GPT+IMT group presented at baseline higher values than GPT group. The meaningful change criteria of the PFSDQ-M appear achievable, because it is comparable with the magnitudes of improvement reported in research studies (77;78). In

addition, previous studies showed significant improvement in functional status after a 3-month rehabilitation program (79;80), with decrease in PFSDQ-M scores that are in line with our results. In addition, we may consider the clinical consequence of the changes obtained in the PFSDQ-M domains after training may also be evaluated by the MID of the PFSDQ-M, which corresponds to a change of -5 points, showing a clinically important improvement (81). The reduction of dyspnea after physical training is one of the most significant predictor of the MID for HRQoL. In our study the MID of BS, MRC and PFSDQ-M (14;73;81) were achieved by the majority of patients, independently of the physical training group.

Further, our results demonstrated significant improvement in measures of PImax (54) with an increase in the inspiratory muscle force in the IMT group, which may explain the improvement of dyspnea score, reported by BS in the ADL set. It is well-known that weakness and the decrease of muscle respiratory endurance cause dyspnea, which can be reversible by IMT (9;10;82). Previous studies (83;84) showed that IMT may enhance respiratory muscle function and reduce dyspnea in patients with moderate-to-severe COPD when compared to a control group. These results are in line with our results within group analysis, such as both groups had a significant rise in the inspiratory muscle force assessed by the PImax, which corroborates other studies (11) and the reference values proposed by Neder et al (54). Furthermore, we can consider a clinically relevant improvement for inspiratory muscle strength (>13cmH_2O) after training (11) in both groups. Decramer in an elegant review concluded that the role of IMT remains unclear due to the absence of clear data on the effects of IMT on outcomes of patients with COPD, such as exercise capacity, functional exercise capacity, and dyspnea during ADL (82).

In accordance with our results, we suggest that even if there was no specific ADL training, the dyspnea symptom and functional status were well improved after both physical trainings, which corroborate the scales and questionnaire findings, as the functional disability related to

ADL, associated with dyspnea can be evaluated through them, which contain simple questions (14;15;17-19;67) that might be compared with our adapted ADL set.

Clinical Relevance

Our study provided information to judge the impact of patient reported outcomes and different training protocols on symptoms reduction at ADL performance.

Limitation of the study

Limitations in the study should be considered. As a preliminary result, the sample size of 40 (20 per group) would yield 80% power (α= 0.05) to detect a between-group difference based on 1.0 point in Borg Dyspnea rating (14) sample size was not met as we were unable to recruit sufficient number of patients to complete the program on time. Furthermore, although we used reliable tools to evaluate patient ability to carry out ADL such as the 6MWT and had simulated an ADL set, we did not have an activity monitor to quantify these activities. Moreover, we did not do a special training based on them. These factors might have influenced the results or/and the amount of benefits in the specific training.

Conclusion

In conclusion the scales and questionnaire assessed: BS, MRC, LCADL and PFSDQ-M were able to detect changes in dyspnea and functional status in both groups after 4 month-rehabilitation in patients with COPD. Additionally, the instruments which have close association with ADL (LCADL and PFSDQ-M) were able to show major change in dyspnea. Furthermore, the GPT+IMT group reported more responsiveness of dyspnea fall in all assessed instruments.

Clinicaltrials.gov number NCT01510041

Tables

Table 1. Baseline characteristics, time of ADL protocol and 6MWD of both groups: General physical training and General physical training associated with inspiratory muscle training.

Variables	GPT Mean ± SD or median[IQI] n=13	GPT+IMT Mean ± SD or median [IQI] n=15
Gender (male/female)	11/2	14/1
Age (yrs)	67.1±7.3	67.4± 11.7
BMI (kg/m^2)	23.7±3.2	22.2± 3.1
FEV_1 (% pred)	43.0±4.0	51.0± 3.0
FVC (% pred)	66.4±13.9	70.8±17.2
PImax (cmH_2O)	57.0±15.0	50.6±20.5
MRC	1[1-2]	2[1-2]
ADL set (s)	2292.9±475.2	2395.6±551.6
6MWD (m)	478.3±26.1	435.3±89.2

GPT= General physical training; GPT+IMT= General Physical Training plus Inspiratory muscle training; SD = standard deviation; [IQI] = interquartile interval; BMI= body mass index; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; PImax= maximum inspiratory pressure; MRC=Medical research council scale; ADL= Activity of daily living; 6MWD = six minute walking distance.

Table 2. Within and between groups' analysis: General Physical training and General physical training associated with inspiratory muscle training. Baseline versus 16 weeks program.

Variables Median [IQI] or Mean±SD	GPT Baseline	GPT 16 weeks program	p-value	GPT+IMT Baseline	GPT+IMT 16 weeks program	p-value
MRC	1[1-2]	1[1-1]	0.060	2[1-2]	1[1-1]*	0.007
LCADL (points)						
self-care	7[6-9]	5[4-5.75]*	0.005	6[5-6.25]	4[4-4.25]*	0.05
Domestic	9.5[5-12]	5[5-6]*	0.01	8[6.5-12]	5[5-6]*	0.02
Physical	4[3-5.75]	3[3-4]*	0.05	6[4-7]	2[2-3]*	0.01
Leisure	4[4-5.75]	3[3-4.5]*	0.02	7[5-8]	3[3-3]*	0.01
Total	27.5[18-33.25]	17[16-18]*	0.003	17[13-19.5]	14[14-15]*	0.02
PFSDQ-M (points)						
activity	25[15-39]	9[5-12]*	0.002	48[40-55.5]	9[9-13.5]*†	0.001
dyspnea	33[23-41]	11[6-12]*	0.002	54[49.5-60.5]	8[7-10]*†	0.001
Fatigue	9[5-13]	3[1-5]*	0.003	15[12.5-17.5]	3[1-5]*	0.003
BS – ADL						
making bed	2[1-2]	0[0-1]*	0.050	2[1-3]	0[0-1]*	0.051
taking shower	3[1-3]	1[0-1]*	0.037	3[2-4]	1[0-2]*	0.050
brushing teeth and combing hair	2[1-3]	1[0-1]*	0.050	3[2-4]	1[0-1]*	0.050
lifting and lowering containers on a shelf above eye level	3[1-3]	1[0-2]*	0.050	3[2-4]	1[0-1]*	0.054
lifting and lowering containers on a shelf below the pelvic waist	3[1-3]	1[0-1.5]*	0.050	4[2-4]	1[0-1]*	0.023
PImax (cmH_2O)	57.0±15.0	75.3±9.6ᵠ	0.05	50.6±20.5	82.6±22.5ᵠ†	0.01

p<0.05 *Wilcoxon, ᵠ Pared t test, †Kruskal-Wallis. GPT= General physical training; GPT+IMT= General Physical Training plus Inspiratory muscle training; [IQI] = Interquartile interval; MRC=Medical Research Council scale; LCADL= London Chest Activity of Daily Living; PFSDQ-M = Pulmonary Functional Status and Dyspnea Questionnaire - Modified version; BS = Borg scale; ADL=Activity of Daily Living.

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CHAPTER 4: STUDY III

The Minimal Important Difference of the Pulmonary Functional Status and Dyspnea Questionnaire - Modified version in Patients with Chronic Obstructive Pulmonary Disease.

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Running head: Minimal important difference of the modified PFSDQ

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Abstract

The modified version of the Pulmonary Functional Status and Dyspnea Questionnaire (PFSDQ-M) is commonly used in patients with COPD to obtain information about their functional status. It consists of 3 components (change in activities, dyspnea and fatigue) ranging from 0 to 100 and has shown to be responsive following pulmonary rehabilitation (PR). The interpretation of changes in PFSDQ-M score after an intervention is difficult in the absence of minimal important difference (MID) of the PFSDQ-M. This study aims at investigating the MID of the PFSDQ-M.

We enrolled 301 patients with COPD (FEV_1 42±15%pred) that completed the PFSDQ-M before and after a 3-month PR (ΔChronic Respiratory Disease Questionnaire (CRDQ) +16±12points, ΔSix-minute walking distance (6MWD) +47±89m, both $p<0.001$). An anchor-based approach consisted of calculating the correlation between the DPFSDQ-M and anchors with an established MID (ΔCRDQ and Δ6MWD). Linear regression analysis were performed to predict the MID from those anchors. Secondly, several distribution-based approaches (Cohen's effect size, empirical rule effect size and standard error of measurement method) were used.

Anchor-based estimates for the different PFSDQ-M-components were between -3 and -5 points based on CRDQ score and -6 (only calculated for change in activities) based on 6MWD. Using the distribution-based methods, the estimates of MID ranged from -3 to -5 points for the different components.

We concluded that the estimate of MID of the PFSDQ-M after pulmonary rehabilitation corresponds to a change of 5 points (range - 3 to -6) in each component in patients with moderate to very severe COPD.

Introduction

Patients suffering from chronic obstructive pulmonary disease (COPD) have low spontaneous levels of daily physical activity and impaired exercise performance (69). They typically experience symptoms of dyspnea and fatigue when performing activities of daily life (ADL). Consequently, improving the patient's functional status and symptoms during ADL is an important goal for treatment (69;70). The Pulmonary Functional Status and Dyspnea Questionnaire (PFSDQ) is an instrument designed to quantify the experienced change in performing ADL compared to the period before disease onset and symptoms of dyspnea related to ADL (71). The modified version of the PFSDQ (PFSDQ-M) includes an additional component about fatigue during ADL (19). The components of the PFSDQ-M are assessed evaluating ten common activities, *e.g.* putting on a shirt, walk on ramps and climbing three stairs. The magnitude of change in the questionnaires, (*e.g.* PFSDQ-M scores) after an intervention is difficult to interpret in the absence of the orientation on what constitutes an important difference for this patient reported outcome (27;85).

The minimal important difference (MID) (86) of a specific instrument can be defined as "the smallest difference in score in the domain of interest that patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient's management" (87). Determination of the MID is important for several reasons, as it facilitates judging the magnitude of the benefit when comparing two treatments, calculating sample sizes, making inferences about the percentages of patients improved by a therapeutic intervention (*e.g.* the number needed to treat), and making cost effectiveness comparisons (30). Currently it is unknown which change in PFSDQ-M score can be considered as a clinically relevant change. Establishing the threshold of MID for the PFSDQ-M would add to the interpretation of the improvement of dyspnea and fatigue symptoms and change in ADL after a pulmonary rehabilitation (PR) program (31;32).

The aim of this study was to establish the MID of the PFSDQ-M in patients with COPD using an anchor and distribution-based approach.

Methods and Materials

Subjects

Four hundred and sixteen patients with moderate to very severe COPD participated in the outpatient PR program in the University Hospital Gasthuisberg in Leuven-Belgium in the period from March 2000 to July 2010. We enrolled the 301 patients who completed the interviewed version of the PFSDQ-M before and after the program. In addition, test-retest reliability was evaluated in 20 patients with COPD using a one-week interval between assessments.

The study protocol was approved by the ethics committee of University Hospital Gasthuisberg, Leuven (project number B322201110245) (Attachment III). Written informed consent was obtained from all patients.

Study design

Data were retrieved from the PR database of the hospital where data at entry and follow up of PR are systematically recorded. The patients followed a 3-month multidisciplinary pulmonary rehabilitation program according to international guidelines (31;88). The program included three weekly 90-minute exercise training sessions. Besides exercise training the program consisted of individual sessions with a psychotherapist, an occupational therapist, a nutritional specialist, a nurse and a social worker. Lung function, respiratory and peripheral muscle strength, functional and maximal exercise capacity, health-related quality of life and the PFSDQ-M were assessed before and after the program.

Assessment of Pulmonary Functional Status and Dyspnea Questionnaire – Modified version

The PFSDQ-M consists of three components: dyspnea, fatigue and change in activities experienced by patients compared to the period before disease onset in 10 common activities (19). The five general survey questions in the dyspnea and fatigue components are considered informative and qualitative and these answers are not further analyzed. For each component, each activity is scored on an 11 point scale ranging from 0 to 10. Ratings on the dyspnea and fatigue component range from 0 "No shortness of breath/fatigue" to 10 "Very severe shortness of breath/fatigue" performing the specific activities. The change component is also rated on an 11 point scale from 0 "As active as I've ever been" to 10, "Have omitted entirely (the activity)". Dyspnea component and fatigue component scores from 1-3 are labeled as mild, scores from 4-6 moderate and scores from 7-9 severe symptoms. Change component scores from 1-3 are labeled as a minor change, 4-6 a moderate change and 7-9 an extreme change in functional performance. For each of the three components a score (ranging from 0 to 100) is calculated, with lower scores indicating a better functional status. We also computed a total score (sum of scores of the 3 components) to divide patients in tertiles based on baseline functional status. The questionnaires were administered by the occupational therapist of the multidisciplinary pulmonary rehabilitation program as part of its baseline and follow-up assessment.

Anchor and Distribution Based Methods

Different methods were used to determine the MID of the PFSDQ-M: one anchor-based method with two clinical anchors related to functional status (Chronic Respiratory Disease Questionnaire (CRDQ) and the six-minute walking distance (6MWD)) and three distribution-based methods (Cohen's effect size (Cohen's ES), empirical rule effect size (ERES) and standard error of measurement (SEM) method).

Anchor Based Method

Using linear regression analyses, the known MID of the anchor was used to determine the corresponding minimal important change of the different PFSDQ-M components (85). We used anchors that have been previously validated in patients with COPD: the CRDQ (25) and the 6MWD (23;25) .

The CRDQ is a widely used instrument in respiratory rehabilitation used to assess health-related quality of life (89). The twenty-item questionnaire scores quality of life in 4 domains which are dyspnea, fatigue, emotional functioning and mastery (90). A change of 0.5 per item within each domain was suggested as being the MID of the CRDQ (30;91-93). Therefore if all questions within a domain are answered, the clinically important difference for each domain is as follows: dyspnea 2.5, fatigue 2.0, emotional function 3.5 and mastery 2.0 points. A change of 10 points in the total score for the CRDQ is considered the MID. The interviewed Dutch version was used in this study (94). The dyspnea and fatigue domains and the total score of the CRDQ were used as anchors.

The 6MWD is a standardized measure of functional exercise capacity in patients with COPD. The distance walked is associated with clinical outcomes. Changes in 6MWD are used to evaluate the efficacy of therapeutic interventions such as pulmonary rehabilitation(23) . In a recent study Puhan et al. established a change of approximately 35m as a MID of 6MWD(95). We followed a similar methodology in our study. The 6MWD test was performed in a 50m corridor. Standardized encouragement was provided. The best result of two tests was used for analysis (96).

For the analysis we assessed the correlation between changes in the anchors and changes in the PFSDQ-M component scores. In addition, we used a linear regression analyses with PFSDQ-M component scores as the dependent and the anchors as independent variables if correlation coefficients were ≥ 0.3(25). Using the regression equation and the MID of the

anchors (0.5 points for each domain and 10 points for total score in the CRDQ and 35m for the 6MWD) we estimated the MID of PFSDQ-M component scores.

Distribution based methods

We used the standard deviation (SD) of change in PFSDQ-M score after the rehabilitation program to calculate Cohen's ES and ERES. According to Cohen, 0.5 x SD units represent a moderate effect size and investigators usually consider this estimate to correspond to an important effect (97). The ERES approach uses the empirical rule that in a normal distribution 99% of all observations lie within 3 SD below and above the mean. A change of 0.5 SD units corresponds to an 8% change within the normal distribution. According to the ERES approach, 8% of the observed range (from the 0.5^{th} to the 99.5^{th} percentile) corresponds to an important effect. The SEM method multiplies SD of the baseline score with $\sqrt{(1-r)}$, where r is the test-retest reliability coefficient (intra-class correlation coefficient (ICC)) of the PFSDQ-M (98).

Statistical analyses were performed with SAS 9. 2. V.2 statistical package.

Results

Baseline characteristics of 301 patients used to assess the MID and 20 patients used to investigate test-retest reliability are reported in Table 1.

Anchor-based approach

Table 2 shows baseline values and change after rehabilitation for PFSDQ-M and CRDQ scores and 6MWD. The correlations between changes in PFSDQ-M component scores and changes in the anchors are also included in Table 2. Figure 1 provides the distribution of the change in PFSDQ-M dyspnea score after rehabilitation. Similar results were obtained for the other components. The change scores for the CRDQ and 6MWD both exceeded their established MID (0.5 point per item, and 10 points total score, and 35 meters, respectively).

Correlations ≥ 0.3 were found between the change in PFSDQ-M components with change in CRDQ dyspnea and total score. Only the change in activity component of PFSDQ-M showed a correlation ≥ 0.3 with change in 6MWD (Table 2). The relationship between change in activity component scores and change in the anchors (6MWD and CRDQ total score) is illustrated in Figure 2. Correlations between change in PFSDQ-M components and change in the CRDQ fatigue domain were < 0.3. Table 3 shows the MID (95% CI) estimates based on the anchor-based method. The estimation of the MID was consistent across the seven regression models (correlation ≥ 0.3)(25) and ranged from -3.2 to -5.9 points. For the 6MWD table 3 also provides the regression equation between PFSDQ-M and the 6MWD as there are several proposed thresholds for the MID of the 6MWD test. Using the regression equation ΔPFSDQ-M = -(0.03 * Δ6MWD) - 5.06 the MID of PFSDQ-M would be - 6,1 points using 35m and -6.7 points using 54m as MID of the 6MWD test. When applying the Cohen's effect size method to our patient group, our estimate of MID of the 6MWD test would be 44.5, which corresponds to an MID of -6.3 points for the PFSDQ-M.

To investigate whether changes in PFSDQ-M were influenced by the baseline functional status, we divided patients in three tertiles based on baseline PFSDQ-M total score (lower tertile: score ≤ 112; middle tertile: 112 < score < 162; higher tertile: ≥ 162) with the lower tertile representing those patients with the best preserved functional status. Changes in PFSDQ-M per tertile are shown in Figure 3 for the dyspnea component. Similar graphs are obtained for the change in activities and fatigue components. No significant differences in change of PFSDQ-M components were found between tertiles.

Distribution-based approach

The ICC between test and retest was 0.79 for the change in activity component and 0.77 for dyspnea and fatigue components of PFSDQ-M. Table 4 shows the MID estimates using the

distribution-based methods Cohen's ES, ERES and SEM**.** The MID of PFSDQ-M using these techniques ranged from – 3.1 to – 4.7 points**.**

Discussion

This is the first study to determine the minimal important difference of the modified version of the PFSDQ in patients with moderate to very severe COPD using different approaches based on state-of-the-art analytic techniques (99). Our estimates for the minimal important difference of the different PFSDQ-M components ranged from -3 to -6 points with anchor-based methods (using CRDQ dyspnea and total score and 6MWD as anchors) and from -3 to -5 points using different distribution-based methods (Cohen's effect size, empirical rule effect size and the standard error of measurement method).

Anchor and distribution based method are conceptually very different (27). Regardless of the apparent differences between methods, there is evidence that diverse methods yield apparently similar findings (100;101).

Despite the low correlation found between changes in the target instrument and changes of the anchors, the consistency of the result using different techniques to establish the MID and our large sample size (23;99) support the validity of our findings. As a consequence of the low correlation coefficient (< 0.3)(25) between the instruments we could not use the CRDQ fatigue domain as an anchor, neither the 6MWD for the PFSDQ-M dyspnea and fa**t**igue component.

Estimates of the magnitude of clinically meaningful change in physical performance measures can contribute to the needs of clinical and research outcomes (99) of interventions. Functional status assessment is an important aspect in evaluating the patient's ability to perform daily activities and the PFSDQ-M is one of the most commonly used tools. The PFSDQ-M is a reliable and valid questionnaire (19;25) . In addition, it has been shown to be

responsive to changes following pulmonary rehabilitation(25) and based on our data changes are independent of baseline functional status. The present study allows putting the effects in a context of clinical relevance in future studies.

We suggest that when a group of patients decrease their PFSDQ-M score around 5 points this would be indicative of a clinically significant improvement of functional status. Estimations of the MID were similar in subgroups of patients with different baseline functional status. A change of -5 points corresponds approximately to a 12 % change from the baseline scores and 5% of the range. This % of the range is in line with that observed in other questionnaires (e.g. SGRQ; MID of 4 points corresponds with 4% of the range) (102). Other studies using other interventions may further fine tune the minimal important difference of the PFSDQ-M (103). Others have also found it difficult to confirm a MID between different interventions (104).

The PFSDQ-M is an instrument used in pulmonary rehabilitation that provides information about patient's symptoms and their functional performance(19). The meaningful change criteria of the PFSDQ-M appear achievable, because it is comparable with the magnitudes of improvement reported in research studies (77;78). In addition, previous studies showed significant improvement in functional status after 3-month rehabilitation program (79;80), with decrease in PFSDQ-M scores that are in line with our results.

The estimates of change should be considered as preliminary evidence and will require further confirmation using similar as well as additional techniques. Patient ratings that could reflect perceived changes in exercise capacity and functional performance have also been used to identify minimal clinically important differences in previous studies (2;24;104). However this technique may be biased by poor recollection and particularly changes in expectations when patients have to judge on themselves over a large period of time.

Clinical relevance

Our study provides a framework to judge impact of rehabilitation interventions on this patient reported outcome. It also provides a benchmarking for clinical rehabilitation programs using this outcome to assess efficacy.

Conclusion

The minimal important difference of the PFSDQ-M corresponds to a change of -5 points (range - 3 to -6 points) in patients with COPD on a scale ranging from 0 to 100 in each component. This estimate was confirmed by both anchor and distribution - based methods and seems relatively stable across baseline functional status. The PFSDQ-M is capable of capturing change in functional status over time. Further studies are necessary to evaluate whether the MID of PFSDQ-M remains stable in earlier stages of COPD.

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Ms Regueiro: contributed to conceiving and designing the study, collecting the data, interpreting the data, writing the manuscript, and approving the final version of the manuscript.

Mr Burtin: contributed to training the patients, conceiving and designing the study, collecting, analyzing and interpreting the data, providing critical revisions that are important for the intellectual content, and approving the final version of the manuscript.

Mr Baten: contributed to collecting the data, providing critical revisions that are important for the intellectual content, and approving the final version of the manuscript.

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Prof Pires Di Lorenzo: contributed to providing critical revisions that are important for the intellectual content, and approving the final version of the manuscript.

Prof Costa contributed to providing critical revisions that are important for the intellectual content, and approving the final version of the manuscript.

Dr Janssens: contributed to interpreting the data, providing critical revisions that were important for the intellectual content, and approving the final version of the manuscript.

Dr Decramer: contributed to interpreting the data, providing critical revisions that were important for the intellectual content, and approving the final version of the manuscript.

Prof Gosselink: contributed to conceiving and designing the study, interpreting the data, providing critical revisions that are important for the intellectual content, and approving the final version of the manuscript.

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Figures and legends

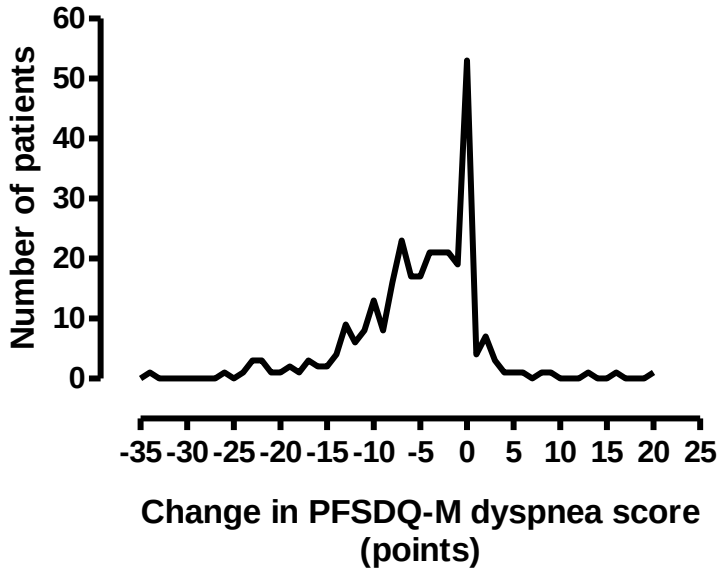

Figure 1. Frequency distribution of the change in PFSDQ-M dyspnea score after a 3-month pulmonary rehabilitation program.

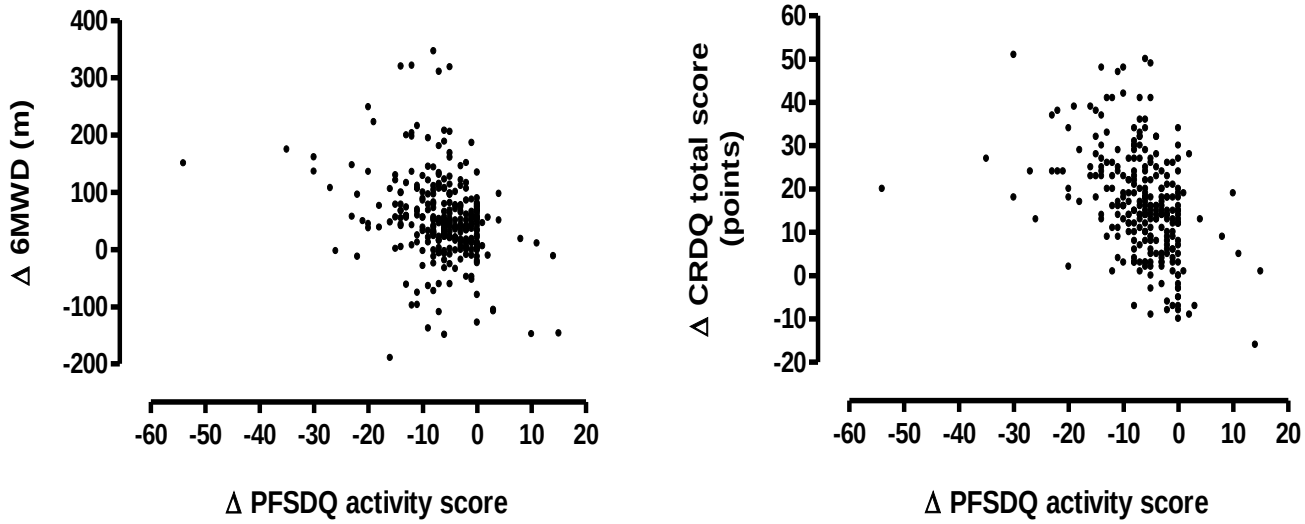

Figure 2. Relationship between changes in activity domain score of PFSDQ-M and 6MWD (2A; r = -0.30, p<0.001) and CRDQ total scores (2B; r = -0.42, p<0.001) after the rehabilitation program.

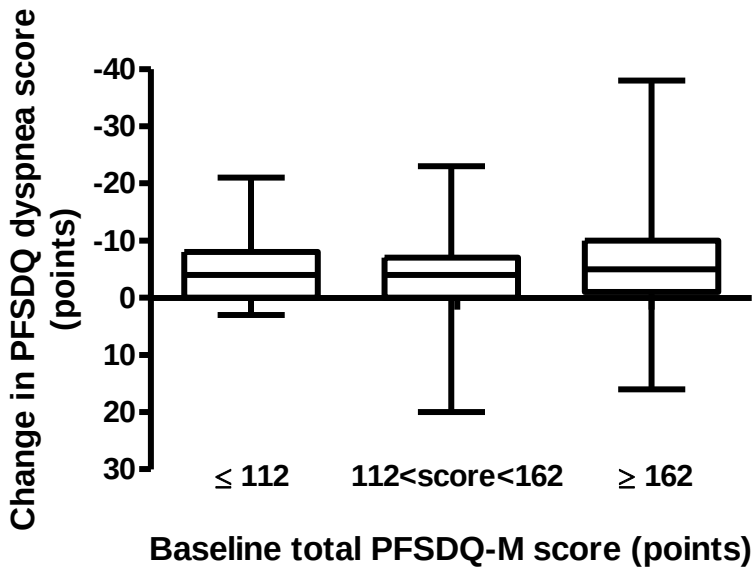

Figure 3. Box plots of change in the dyspnea component of PFSDQ-M after 3 months of pulmonary rehabilitation related to baseline functional status. Patients are divided in 3 tertiles based on baseline total PFSDQ-M score (lower tertile: ≤ 112; 112 < middle tertile < 162; higher tertile: ≥ 162 points; the lower tertile represents those patients with the best preserved functional status). No significant differences were observed between tertiles. Similar results were obtained for change in activities and fatigue components of PFSDQ-M.

Tables

Table 1. Baseline characteristics of the enrolled patients.

Variables	Mean ± SD n=301	Test-retest analyses n=20
Gender (male/female)	241/60	15/5
Age (yrs)	65±7	68± 6
BMI (kg/m^2)	25±5	27± 6
FEV_1 (% pred)	42±15	52± 11
FVC (% pred)	85±20	104± 18
FRC (% pred)	156±36	164± 37
TLC (% pred)	113±18	124± 25
$TL_{,CO}$ (% pred)	47±16	27± 6
PImax (% pred)	77±26	75±12
VO_2 max (ml/kg/min)	14±6	14±4
W max (% pred)	64±25	78±20
6MWD (m)	396±124	510±85
PFSDQ-M activity (points)	47±17	29±18
PFSDQ-M dyspnea (points)	48±17	28±20
PFSDQ-M fatigue (points)	42±19	24±20

SD = standard deviation; BMI= body mass index; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; FRC= functional residual capacity; TLC=total lung capacity; $TL_{,CO}$ = transfer factor of carbon monoxide; PImax= maximum inspiratory pressure; 6MWD = six minute walking distance; PFSDQ-M = pulmonary functional status and dyspnea questionnaire modified version.

Table 2. Baseline values, changes and correlations of changes in PFSDQ-M and CRDQ scores and 6MWD from baseline to 3-months rehabilitation program.

		N=301	PFSDQ-M activity component	PFSDQ-M dyspnea component	PFSDQ-M fatigue component
	Baseline values	**∆Changes from baseline to 3-month PR**	- 6±7	- 5±7	- 5±7
CRDQ dyspnea	15±4	6±5	- 0.32*‡	- 0.30*‡	- 0.34*‡
CRDQ fatigue	15±4	3±3	- 0.27‡	- 0.23 ‡	- 0.21‡
CRDQ total	78±16	16±12	- 0.42*‡	- 0.41*‡	- 0.41*‡
6MWD (m)	396±124	47±89	- 0.30*‡	- 0.26‡	- 0.27‡

Data for changes are expressed in mean ± SD. SD = standard deviation; PR = pulmonary rehabilitation; PFSDQ-M = pulmonary functional status and dyspnea questionnaire modified version; CRDQ = chronic respiratory disease questionnaire; 6MWD = six minute walking distance.
Pearson correlation coefficient; ‡p<0.0001.*Values indicate sufficient correlation for using the anchor based method (linear regression analyses).

Table 3. Anchor - based method to determine the minimal important difference of the PFSDQ-M.

Anchor	MID of PFSDQ-M (95% CI)	Score PFSDQ-M Component
CRDQ dyspnea score (MID =0.5 per-item x 5 item)	- 5.0 (- 6 to - 3)	Activity
	- 4.0 (- 5 to - 2)	Dyspnea
	- 3.2 (- 4 to - 1)	Fatigue
CRDQ total score (MID = 10)	- 4.9 (- 7 to - 2)	Activity
	- 4.0 (- 6 to - 1)	Dyspnea
	- 3.3 (- 5 to - 1)	Fatigue
6MWD (MID = 35m)	- 6,1 (- 7 to - 5)	Activity

MID = minimal important difference; PFSDQ-M= pulmonary functional status and dyspnea questionnaire modified version; CRDQ = chronic respiratory disease questionnaire; 6MWD = six minute walking distance.

Table 4. Distribution - based method to determine the minimal important difference of the PFSDQ-M.

Distribution based method	MID of PFSDQ-M
Cohen effect size	
Activity	- 3.6
Dyspnea	- 3.7
Fatigue	- 3.5
Empirical rule effect size	
Activity	- 4.0
Dyspnea	- 4.3
Fatigue	- 4.7
Standard error of measurement	
Activity	- 3.2
Dyspnea	- 3.3
Fatigue	- 3.1

MID = minimal important difference; PFSDQ-M = pulmonary functional status and dyspnea questionnaire modified version.

CHAPTER 5: FUTURE DIRECTIONS

Further researches focusing on the effects of rehabilitation programs with different exercise training modalities, including inspiratory muscle training and instruments to assess dyspnea and it responsiveness to a specific treatment and functional status at activities of daily living with different designs from the ones used in the present thesis are warranted. This might help to find out which type of intervention will be specific and able to improve symptoms and the activities of daily living performance in patients with COPD.

Regarding to the MID, as mentioned previously, this measure might be able to facilitate the judgment of the magnitude of the benefit when comparing two treatments or making inferences about the percentage of patients who had improvements through a therapeutic intervention. It was shown that the PFSDQ-M is capable of reflecting important degrees of change over time and thresholds for meaningful change can be estimated. The scientific literature acquaintance of the MID of the PFSDQ allows benchmarking of rehabilitation programs. However, further studies are necessary to evaluate whether the MID of PFSDQ-M is constant across different pulmonary diseases and levels of disease severity. The estimates of change should be considered as preliminary evidence and will require further confirmation using similar, as well as additional techniques**.**

ATTACHMENTS

ATTACHMENT I: Approval protocol by the ethics committee of Universidade Federal de São Carlos - UFSCar, São Carlos, Brazil to Studies I and II.

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CAAE 0196.0.135.000-09

Título do Projeto: Avaliação das atividades da vida diária por diferentes instrumentos na doença pulmonar obstrutiva crônica
Classificação: Grupo III
Procedência: Departamento de Fisioterapia
Pesquisadores (as): Eloisa Maria Gatti Regueiro, Valéria Amorin Pires Di Lorenzo (orientadora)
Processo nº.: 23112.005225/2009-83

Parecer Nº. 140/2010

1. Normas a serem seguidas

• O sujeito da pesquisa tem a liberdade de recusar-se a participar ou de retirar seu consentimento em qualquer fase da pesquisa, sem penalização alguma e sem prejuízo ao seu cuidado (Res. CNS 196/96 – Item IV.1.f) e deve receber uma cópia do Termo de Consentimento Livre e Esclarecido, na íntegra, por ele assinado (Item IV.2.d).
• O pesquisador deve desenvolver a pesquisa conforme delineada no protocolo aprovado e descontinuar o estudo somente após análise das razões da descontinuidade pelo CEP que o aprovou (Res. CNS Item III.3.z), aguardando seu parecer, exceto quando perceber risco ou dano não previsto ao sujeito participante ou quando constatar a superioridade de regime oferecido a um dos grupos da pesquisa (Item V.3) que requeiram ação imediata.
• O CEP deve ser informado de todos os efeitos adversos ou fatos relevantes que alterem o curso normal do estudo (Res. CNS Item V.4). É papel do pesquisador assegurar medidas imediatas adequadas frente a evento adverso grave ocorrido (mesmo que tenha sido em outro centro) e enviar notificação ao CEP e à Agência Nacional de Vigilância Sanitária – ANVISA – junto com seu posicionamento.
• Eventuais modificações ou emendas ao protocolo devem ser apresentadas ao CEP de forma clara e sucinta, identificando a parte do protocolo a ser modificada e suas justificativas. Em caso de projetos do Grupo I ou II apresentados anteriormente à ANVISA, o pesquisador ou patrocinador deve enviá-las também à mesma, junto com o parecer aprobatório do CEP, para serem juntadas ao protocolo inicial (Res. 251/97, item III.2.e).
• Relatórios parciais e final devem ser apresentados ao CEP, inicialmente em ___/___/___ e ao término do estudo.

2. Avaliação do projeto

O Comitê de Ética em Pesquisa em Seres Humanos da Universidade Federal de São Carlos (CEP/UFSCar) analisou o projeto de pesquisa acima identificado e considerando os pareceres do relator e do revisor DELIBEROU:

As pendências apontadas no Parecer nº. 081/2010, de 23/04/2010, foram satisfatoriamente resolvidas.

O projeto atende as exigências contidas na Resolução 196/96, do Conselho Nacional de Saúde.

3. Conclusão:

Projeto aprovado

São Carlos, 6 de maio de 2010.

Profa. Dra. Cristina Paiva de Sousa
Coordenadora do CEP/UFSCar

Impresso em 6/5/2010 10:40:11

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ATTACHMENT II: Written informed consent.

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO
(Consentimento Pós-informação para Pesquisa em Seres Humanos)

Você está sendo convidado a participar da pesquisa *"Avaliação das atividades da vida diária por diferentes instrumentos na doença pulmonar obstrutiva crônica"***.** Aluna Responsável: Ft. Ms.Eloisa Maria Gatti Regueiro. Orientadora: Prof[a]. Dr[a]. Valéria Amorim Pires Di Lorenzo.

Objetivos do estudo

Verificar se há ou não relação do gasto metabólico - ventilatório obtido durante a simulação de atividades de vida diária (AVD) com a dispnéia (falta de ar) avaliada por diferentes escalas e questionário em pacientes com doença pulmonar obstrutiva crônica (DPOC), bem como a monitorização dessas atividades, por meio de um monitor de atividades. Responderei a ficha de avaliação e posso ainda recusar-me a responder qualquer pergunta que me for feita. Para avaliação completa, serei submetido (a) a uma avaliação que constará de uma avaliação clínica fisioterapêutica, exame físico, realização de um circuito de AVD coma simulação de: (1) levantar-se e arrumar a cama; (2) tomar banho e enxugar-se, vestir-se, escovar os dentes e pentear os cabelos; (3) colocar mantimentos e utensílios domésticos em uma prateleira acima da cintura escapular e abaixo da cintura pélvica; (4) Sentar/deitar no sofá, ler jornal/revistas. Além disso, responderei a diferentes questionários e escalas referentes a sensação de falta de ar durante a realização de minhas AVD, como atividades de higiene pessoal, domésticas e de lazer (escala de dispnéia - *Medical Research Council (MRC);*escala *London Chest Activity of Daily Living (LCADL);* escala *Activity of Daily Living Dyspnoea (ADL-D);* e questionário *Pulmonary Functional Status and Dyspnea – Modified version* (*PFSDQ-M*)). Para a realização destas atividades comparecerei a Unidade Saúde Escola (USE) da instituição. Estou ciente ainda, que durante os testes poderei ser fotografado, sendo que minhas imagens serão utilizadas apenas para fins científicos.

O benefício que obterei com tal estudo inclui de uma maneira geral a determinação da minha limitação ao realizar as AVD propostas; com o objetivo de propor um treinamento físico específico futuro e a utilização de técnicas de conservação de energia a fim de melhorar minha qualidade de vida.

Os procedimentos executados durante a simulação das Atividades de Vida Diária (AVD) não evidenciam riscos aos voluntários. Entretanto, se no decorrer dos testes ou após a análise dos resultados for detectada qualquer intercorrência, fui esclarecido que durante toda

a simulação das AVD serão monitorizados devidamente acompanhados com medidas de oximetria de pulso, ausculta pulmonar, frequência cardíaca e pressão arterial, pelo fisioterapeuta especializado; bem como, qualquer sinal ou sintoma que possa representar possíveis riscos como falta de ar e dores nos membros superiores e inferiores por mim relatadas, arritmias, aumento ou queda súbita da pressão arterial, aumento acima da frequência cardíaca máxima prevista para a minha idade e quedas da saturação periférica de oxigênio abaixo de 85%. Visto que como resposta a qualquer esforço físico, há ajustes dos diversos sistemas do organismo que se modificam substancialmente de acordo com a influência de fatores como a idade, sexo, natureza e intensidade da atividade, posição corporal e o grau de condicionamento; entendo que aumentos na frequência cardíaca, frequência respiratória, da ventilação pulmonar e pressão arterial, são variáveis fisiológicas que se alteram durante o esforço e podem se acentuar durante a minha avaliação; mas, retornam a seus valores de base com o repouso; sem que haja prejuízo ou coloque em risco minha saúde.

Eu entendo que não existe nenhum tipo de seguro de saúde ou de vida, bem como qualquer outra compensação financeira que possa vir a me beneficiar em função da minha participação neste estudo.

Fui informado (a) que não terei despesas pessoais relativas à avaliação e tratamento realizados.

Estou ciente ainda, de que as informações obtidas durante todo o tratamento serão mantidas em sigilo e não poderão ser consultadas por pessoas leigas, sem a minha autorização. As informações assim obtidas, no entanto, poderão ser usadas para fins de pesquisa científica, desde que minha privacidade seja sempre resguardada.

Li e entendi as informações precedentes, bem como, eu e os responsáveis pelo projeto já discutimos todos os riscos e benefícios decorrentes deste, sendo que as dúvidas futuras que possam vir a ocorrer, poderão ser prontamente esclarecidas, bem como o acompanhamento dos resultados obtidos durante a coleta dos dados. E, além disso, todas as dúvidas que me ocorreram já foram esclarecidas por completo.

Estou ciente também que poderei desistir de participar do projeto a qualquer momento, mediante aviso prévio ao pesquisador e sem qualquer tipo de ônus a minha pessoa.

Eu estou de acordo com a minha participação neste estudo de livre e espontânea vontade e entendo sua relevância.

Comprometo-me, na medida das minhas possibilidades, prosseguir com as avaliações até a sua finalização, visando além dos benefícios trazidos com estes; colaborar para um bom desempenho do trabalho científico dos responsáveis por este projeto.

O pesquisador me informou que o projeto foi aprovado pelo Comitê de Ética em Pesquisa em Seres Humanos da UFSCar que funciona na Pró-Reitoria de Pós-Graduação e Pesquisa da Universidade Federal de São Carlos, localizada na Rodovia Washington Luiz, Km 235 –Caixa Postal 676 – CEP 13.655-905 – São Carlos, SP _ Brasil. Fone (16) 3351-8111. Endereço Eletrônico: cephumanos@power.ufscar.br

Estando de acordo, eu..... portador (a) do RG n^0....., residente à..... ..... n^0 ....., bairro.....,na cidade de ....., telefone ..... autorizo minha participação na pesquisa "Avaliação das atividades da vida diária por diferentes instrumentos na doença pulmonar obstrutiva crônica".

Para questões relacionadas a este estudo, contate: Eloisa Maria Gatti Regueiro: Fone: (16) 3371-3444; Valéria Amorim Pires Di Lorenzo: fone: (16) 3371-3444; (16) 3351-8343 ou e-mail: vallorenzo@ufscar.com.br. Endereço: Rodovia Washington Luiz, Km 235. Universidade Federal de São Carlos - Laboratório de Espirometria e Fisioterapia Respiratória.

Julgo que é meu direito manter uma cópia deste consentimento.

Assinatura do Voluntário	**Nome por extenso**
Pesquisador Responsável	**Nome por extenso**

São Carlos,.....de.....de .....

Attachment III: Approval protocol by the ethics medical committee of U. Z. Gasthuisberg, Katholieke Universiteit Leuven - KULeuven, Leuven, Belgium to Study III.

COMMISSIE MEDISCHE ETHIEK VAN DE UNIVERSITAIRE ZIEKENHUIZEN KULEUVEN
U.Z. GASTHUISBERG E330
HERESTRAAT 49
B-3000 LEUVEN (BELGIUM)

KATHOLIEKE UNIVERSITEIT LEUVEN

Aan Prof. T. Troosters
Cardiovasculaire en Respiratoire Revalidatie, UZ Leuven

ONS KENMERK ML7060
LEUVEN, 7 januari 2011

The minimal important difference of the pulmonary functional status and dyspnea questionnaire - modified version in patients with chronic obstructive pulmonary disease.

Belgisch Nummer B322201110245

S52929

DEFINITIEF GUNSTIG ADVIES

Geachte Collega,

De Commissie Medische Ethiek van de Universitaire Ziekenhuizen K.U.Leuven heeft vermeld protocol onderzocht en besproken op haar vergadering van 7 januari 2011.

De Commissie is van oordeel dat de voorgestelde studie, zoals beschreven in het protocol, wetenschappelijk relevant en ethisch verantwoord is. Ze verleent dan ook een gunstig advies over deze studie.

Dit gunstig advies betreft onder meer:

- Informatie- en toestemmingsformulier voor de deelnemer: ICF: versie ingediend op 21/12/2010 - Rubriek verzekering: de Commissie raadt aan om de opdrachtgever te specifiëren (= UZ Leuven).
- Protocol: versie 1 : 25/11/2010

De Commissie bevestigt dat ze volgens de ICH-GCP principes werkt (International Conference on Harmonization Guidelines on Good Clinical Practice).

Nota:

Dit gunstig advies van de Commissie houdt niet in dat zij de verantwoordelijkheid voor de geplande studie op zich neemt. U blijft hiervoor dus zelf verantwoordelijk. Bovendien dient U er over te waken dat uw mening als betrokken onderzoeker wordt weergegeven in publicaties, rapporten voor de overheid enz., die het resultaat zijn van dit onderzoek.

U wordt eraan herinnerd dat bij klinische studies iedere door U waargenomen ernstige verwikkeling onmiddellijk zowel aan de opdrachtgever (desgevallend de producent) als aan de commissie medische ethiek moet worden gemeld, ook al is het oorzakelijke verband met de studie onduidelijk.

SECRETARIAAT: M. LEYS N. OPDEKAMP M. SAELENS N. VAN LOOY D. VAN MOLL M. VERBEECK
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BLAD NR . 2

ONS KENMERK ML7060
UW KENMERK
LEUVEN . 7 januari 2011

Indien de studie niet binnen het jaar beëindigd is, vereist de ICH-GCP dat een jaarlijks vorderingsrapport aan de commissie wordt bezorgd.

Tenslotte verzoeken wij U ons mee te delen indien een studie niet wordt aangevat, of wanneer ze wordt afgesloten of vroegtijdig onderbroken (met opgave van eventuele reden).

Indien er een Clinical Trial Agreement is, kan de studie in ons centrum pas aangevat worden wanneer dit Clinical Trial Agreement goedgekeurd en ondertekend werd door de gedelegeerd bestuurder van UZ Leuven.

Met de meeste hoogachting,

Prof. Dr. Walter VAN DEN BOGAERT
Voorzitter Commissie Medische Ethiek
UZ K.U.LEUVEN

Prof. Dr. W. Van den Bogaert
Voorzitter
Commissie Medische Ethiek van de UZ K.U.Leuven

Cc : **FAGG** (Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten)
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