Universidade de Aveiro
2020

Escola Superior de Saúde

ANA QUEIROZ ALVES

Fiabilidade, validade e responsividade do *Chester step test* em pessoas com Doença Pulmonar Intersticial

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Dissertação apresentada à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção do grau de Mestre em Fisioterapia ramo Respiratória, realizada sob a orientação científica da Doutora Alda Marques, Professora Coordenadora da Escola Superior de Saúde da Universidade de Aveiro e da Doutora Ana Oliveira, Investigadora de pós-doutoramento da School of Rehabilitation Sciences, Faculty of Health Sciences, McMaster University.

Esta dissertação integra-se no projeto PRIME - “ Reabilitação respiratória e microbiota nas exacerbações da doença pulmonar obstrutiva crónica (DPOC)”, financiado pelo Programa Operacional de Competitividade e Internacionalização – POCI, através do Fundo Europeu de Desenvolvimento Regional – FEDER (POCI-01-0145-FEDER-007628 e POCI-01-0145-FEDER-028806), Fundação para a Ciência e Tecnologia (PTDC/SAU-SER/28806/2017) e sob o projeto UIDB/04501/2020.

O júri

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Agradecimentos

À minha orientadora, Professora Doutora Alda Marques, pelo acompanhamento, apoio e disponibilidade que sempre demonstrou. Pela oportunidade de me ter integrado numa equipa de investigação genial e pelo crescimento profissional que daí resultou.

À minha co-orientadora, Doutora Ana Oliveira, pela amabilidade, disponibilidade muitíssimo além-fronteiras e ajuda em todos os momentos.

Ao Doutor Pedro Ferreira, pela referenciação dos doentes e disponibilidade no acompanhamento clínico durante todo o projeto.

Aos doentes, por terem aceite participar neste projeto, pela troca de experiências e por me relembrarem todos os dias que amo a profissão que escolhi.

À equipa do Lab3R, e em especial à Filipa, à Cátia e à Patrícia pela paciência para me aturarem, pelo companheirismo e pelos conhecimentos que me transmitiram.

À Cláudia Dias e à sua família, por me terem recebido sempre tão bem e pela companhia nas tardes e noites de trabalho na tese.

À Carolina Vasconcelos, pela amizade e pelas conversas e desabafos de horas.

À Sofia Flora, pelas gargalhadas e apoio incondicional. Por estares presente nos bons e maus momentos. Por mais do que amiga, seres família.

À Gabriela, por tudo. Porque tudo.

E por fim, aos meus pais, irmãos e avós, por serem a melhor família que a vida me podia ter proporcionado. Por me aceitarem tal como sou, por me apoiarem em todas as decisões que tomo e por me incentivarem a procurar aquilo que me faz feliz.

Palavras-chave Doença pulmonar intersticial, exercício, step.

Resumo

Enquadramento: O *Chester step test* (CST) é um teste de campo simples e económico, que requer um espaço físico mínimo para avaliar a tolerância ao exercício. Estas características tornam-no apelativo para ser utilizado em qualquer contexto clínico. No entanto, desconhecem-se as suas características clinimétricas na doença pulmonar intersticial (DPI).

Objetivo: Avaliar a fiabilidade, validade, responsividade e efeito de aprendizagem do CST em pessoas com DPI.

Métodos: Realizou-se um estudo descritivo observacional com pessoas com DPI recrutadas em consulta hospitalar de Pneumologia. Foram agendadas 2 sessões de avaliação separadas por 48-72h com presença de um 2º avaliador numa delas. Na 1ª sessão realizou-se o CST-1 e o teste de marcha dos 6-minutos (TM6M-1) e na 2ª sessão aplicou-se o CST-2 e os seguintes questionários: *modified Medical Research Council* (mMRC) *questionnaire*, *COPD assessement test* (CAT), *St. George's respiratory questionnaire* (SGRQ) e *functional assessment of chronic illness therapy-fatigue scale* (FACIT-FS). Após 12 semanas de um programa de reabilitação respiratória (RR) comunitário, aplicou-se novamente o CST-3, o TM6M-2 e os questionários. A fiabilidade relativa foi avaliada com o coeficiente de correlação intra-classe ($ICC_{1,1}$ e $ICC_{2,1}$). A fiabilidade absoluta foi calculada com o erro standard de medida (SEM), diferença mínima detetável (MDC_{95}) e método de Bland&Altman. Os valores de SEM e MDC_{95} foram ainda expressos como percentagem da média. A validade de construto foi explorada com a correlação de *Spearman* (r_s) entre o melhor CST e o TM6M-1. A responsividade foi avaliada através do cálculo do tamanho do efeito (ES), das médias das diferenças entre o número de steps do CST-1 e CST-3 e da correlação de *Spearman* entre as diferenças no CTS e as diferenças no TM6M, mMRC, CAT, SGRQ e FACIT-FS, antes e após a RR. O efeito de aprendizagem foi avaliado com o teste T de *Wilcoxon* entre o CST-1 e CST-2.

Resultados: 66 pessoas (65,5±12,9 anos; 48,5 %homens; FVC 79,4±18,8pp; DL_{CO} 49,0±18,3pp) participaram no estudo. A fiabilidade relativa foi excelente (ICC=0,95-1,0); bem como a fiabilidade absoluta sem evidência de viés sistemático. O SEM e MDC_{95} foram 11,8 (14,7%) e 32,6 steps (40,7%), respetivamente. A correlação entre o CST e o TM6M foi significativa, positiva e forte (r_s=0,85, *p*=0,00). O tamanho do efeito foi moderado (ES=0,49) e a média das diferenças entre CST-1 e o CST-3 foi significativa (12,6±30,7 steps; 95%CI 1,8-23,5; *p*=0,004). As correlações entre as diferenças no CST e na mMRC e FACIT-FS foram significativas e moderadas (r_s=-0,37 e 0,60, *p*=0,00-0,036). Não se verificaram outras correlações significativas. Não existiram diferenças significativas entre o CST-1 e o CST-2 (*p*=0,055).

Conclusão: O CST parece ser um teste fiável, válido, responsivo e sem efeito de aprendizagem para avaliar a tolerância ao exercício em pessoas com DPI.

Keywords Interstitial lung disease, exercise, step.

Abstract

Background: The Chester step test (CST) is a simple and inexpensive field test, which requires minimal physical space to assess exercise tolerance. Such characteristics make the CST suitable to be used in different settings, however, its clinimetric properties in people with interstitial lung diseases (ILD) are unknown.

Aim: To assess the reliability, validity, responsiveness and learning effect of the CST in people with ILD.

Methods: An observational descriptive study was conducted in people with ILD recruited from routine pulmonology appointments. Participants were asked to attend to 2 assessment sessions, with 48-72 hours apart and with the presence of a 2nd rater in one of the sessions. In the first session CST-1 and 6-minute walk test (6MWT-1) were performed. In the second session, the CST-2 and the following patient-reported outcome measures (PROMs) were applied: modified Medical Research Council (mMRC) questionnaire, COPD assessment test (CAT), St. George's respiratory questionnaire (SGRQ) and functional assessment of chronic illness therapy-fatigue scale (FACIT-FS). After a 12-week community-based pulmonary rehabilitation (PR) programme, the CST-3, the 6MWT-2 and all PROMs were applied. Relative reliability was measured using intraclass correlation coefficient ($ICC_{1,1}$ and $ICC_{2,1}$). Absolute reliability was determined by calculating the standard error of measurement (SEM), the minimal detectable change at 95% confidence interval (MDC_{95}) and Bland&Altman method. The values of SEM and MDC_{95} were also expressed as a percentage of the mean. Construct validity was explored using Spearman correlation coefficient (r_s) between the number of steps taken in the best CST and the distance covered in 6MWT-1. Responsiveness was established by calculating the effect size (ES), the mean difference of steps between CST-1 and CST-3 and the Spearman correlation coefficient between changes in the CST and changes in the 6MWT, mMRC, CAT, SGRQ and FACIT-FS before and after the PR programme. The learning effect was explored with Wilcoxon T-test to compare the CST-1 and CST-2.

Results: 66 patients with ILD (65.5±12.9 years; 48.5%men; FVC 79.4±18.8pp; DL_{CO} 49.0±18.3pp) participated in the study. Relative reliability was excellent (ICC 0.95-1.0), as well as absolute reliability without evidence of systematic bias. The SEM and MDC_{95} were 11.8 (14.7%) and 32.6 steps (40.7%), respectively. The correlation between CST-1 and 6MWT-1 was significant, positive and high (r_s=0.85, *p*=0.00). The ES was large (ES=0.49) and the mean difference between CST-1 and CST-3 was significant (12.6±30.7 steps; 95%CI 1.8-23.5; *p*=0.004). The correlations between changes in the CST and changes in the mMRC and FACIT-FS were significant and moderate (r_s=-0.37 and 0.60, *p*=0.00-0.036). No other significant correlations were found. There was no statistically significant difference CST-1 and CST-2 (*p*=0.055).

Conclusion: The CST seems to be a reliable, valid, responsive test with no learning effect test to evaluate exercise tolerance in people with ILD.

Abbreviations and/or acronyms

1-RM – One-repetition maximum

6MST – 6-minute step test

6MWD – Distance covered in 6-minute walk test

6MWT – 6-minute walk test

LoA95 – 95% limits of agreement

BMI – Body mass index

BMS – Between subjects mean squares

Brief-BESTest – Brief-balance evaluation systems test

CAT – COPD assessment test

CHP – Chronic hypersensitivity pneumonitis

CI – Confidence interval

COPD – Chronic obstructive pulmonary disease

COSMIN – COnsensus-based Standards for the selection of health status Measurement INstruments

CPET – Cardiopulmonary exercise test

CST – Chester step test

DL_{CO} – Diffusion capacity for carbon monoxide

EMS – Error (residual) mean squares

ES – Effect size

ERS – European Respiratory Society

FACIT-FS – Functional assessment of chronic illness therapy – fatigue scale

FEDER – Fundo Europeu de Desenvolvimento Regional

FEV_1 – Forced expiratory volume in one second

FVC – Forced vital capacity

HR – Heart rate

HRmax – Maximum heart rate

ICC – Intraclass correlation coefficient

ICF – International Classification of Functioning, Disability and Health

IIP – Idiopathic interstitial pneumonias

ILD – Interstitial lung disease

IPF – Idiopathic pulmonary fibrosis

ISWT – Incremental shuttle walk test

k – Number of measurements/raters

KS – Kolmogorov-Smirnov test

Lab 3R – Respiratory Research and Rehabilitation Laboratory of the School of Health Sciences, University of Aveiro

MCID – Minimal clinically important difference

MDC_{95} – Minimal detectable change with a 95% interval confidence

mMRC – modified Medical Research Council questionnaire

n – Number of participants

N – Number of total match pairs

POCI – Programa Operacional de Competitividade e Internacionalização

PR – Pulmonary Rehabilitation

PRIME – Pulmonary Rehabilitation Innovation and Microbiota in Exacerbations of COPD

PROMs – Patient-reported outcome measures

r – Pearson correlation coefficient

r_s – Spearman's correlation coefficient

RMS – Between raters mean squares

SCQ – Self-administered comorbidities questionnaire

SD – Standard deviation

SEM – Standard error of measurement

SGRQ – St. George's respiratory questionnaire

SpO_2 – Blood oxygen saturation

UICISA: E – Unidade de Investigação em Ciências da Saúde: Enfermagem

$VO2_{peak}$ – Peak oxygen consumption

$VO_{2\ estimated}$ – Estimated peak oxygen uptake

WMS – Within subjects mean squares

W_{peak} – Work peak

Z – Statistic Wilcoxon T-test

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1. Introduction

Interstitial lung diseases (ILD) are a heterogeneous group of diffuse parenchymal lung disorders (1). More than 300 different types of ILD have been identified, but the most common types are idiopathic pulmonary fibrosis (IPF), chronic hypersensitivity pneumonitis (CHP), sarcoidosis, idiopathic interstitial pneumonias (IIP) and ILD associated with connective tissue disease (2, 3). Accurate estimates of the prevalence of ILD are yet unknown however, in Europe, the estimated prevalence of IPF and sarcoidosis is 27 and 15 cases per 100 000 individuals/year, respectively (2). Although considered rare diseases, some patients exhibit an accelerated decline of their health status with high associated socioeconomic costs, resulting in a median survival rate below 5 years, an huge dependency on others to perform daily living activities and a massive burden for healthcare systems (4-7).

Despite presenting diverse aetiologies, people with ILD share several clinical features (5, 8-10). Most patients develop chronic progressive fibrosis and lung inflammation, leading to impairments in gas exchange, restrictive physiology (2, 5, 9, 10), exertional dyspnoea, dry cough, fatigue and reduced exercise tolerance that severely limit their daily living activities and restrict social life (5, 10-12). In people with ILD, reduced exercise tolerance is associated with poor health-related quality of life and substantial morbidity and mortality (1, 13). Thus, improving exercise tolerance in this population has become a priority for healthcare professionals (14). Pulmonary rehabilitation (PR) is a safe, comprehensive, multidisciplinary and evidence-based approach, that includes exercise training, education and behaviour modification (13). Currently, it is pointed as the most widely used, cost-effective and meaningful non-pharmacological management strategy for most patients with ILD, as it has demonstrated to improve their symptoms, exercise tolerance and health-related quality of life (3, 13).

The gold standard to evaluate exercise capacity is cardiopulmonary exercise testing (CPET), which allows to directly measure peak oxygen consumption ($VO_{2\ peak}$), determines exercise-related symptoms and provides relevant information for clinical decision making and exercise prescription (15). However, CPET is not easily available in clinical practice as it requires expensive equipment, the presence of specialised human resources and is time-consuming (16). To overcome these limitations, field tests such as the 6-minute walk test (6MWT), the incremental shuttle walk test (ISWT) and, more recently, the Chester step test (CST) have been used to predict exercise capacity in patients with chronic respiratory

diseases (16-18). These tests are more affordable and simple to apply than CPET and are better related to patients' demands during activities of daily living (18, 19). The CST also requires less space than the other field tests, which allows it to be easily applied in different settings, including inpatient, outpatient and home-based settings (19).

The CST is an externally paced, incremental and multistage test, designed to assess exercise capacity in healthy individuals (16, 19). Recently, it has been validated to assess exercise capacity and to estimate peak oxygen uptake ($VO_{2\ estimated}$) in patients with chronic obstructive pulmonary disease (COPD) (16). However, the physiological mechanisms of exercise limitation in patients with COPD differ significantly from those in patients with ILD, in whom exercise intolerance is mostly due to impaired gas exchange and circulation limitation (13, 14). Thus, it is imperative to test the CST for its measurement properties in this specific population, namely for its reliability, validity and responsiveness to therapy, so we can assure that the selection of this instrument is evidence-based, recommended to use in clinical practice and that we interpret the results obtained with confidence (20).

According to our best knowledge, there are no studies in patients with ILD evaluating the measurement properties of the CST. Thus, the main purpose of this study was to assess the reliability (relative and absolute), construct validity and responsiveness of the CST in patients with ILD, after a 12-week community-based PR programme. Secondarily, we aimed to investigate the presence of learning effect in the CST.

The authors hypothesized that the number of steps in the CST will present: (1) excellent intra and inter-rater reliability; (2) significant, positive and high correlation with the distance covered in the 6MWT (6MWD) and (3) absence of learning effect. Additionally, after PR, we hypothesize that changes in the number of steps in the CST will present (4) moderate effect size (ES); (5) significant, positive and weak correlation with changes in the 6MWD; (6) significant, negative and weak correlations with changes in the modified Medical Research Council questionnaire (mMRC), COPD assessment test (CAT), St. George's respiratory questionnaire (SGRQ) and (7) significant, positive and moderate correlations with changes in the functional assessment of chronic illness therapy – fatigue scale (FACIT-FS).

2. Methods

This work is part of a larger study entitled "Pulmonary Rehabilitation Innovation and Microbiota in Exacerbations of COPD – PRIME", funded by *Programa Operacional de Competitividade e Internacionalização* – POCI, through *Fundo Europeu de*

Desenvolvimento Regional - FEDER (POCI-01-0145-FEDER-007628 and POCI-01-0145-FEDER-028806), *Fundação para a Ciência e Tecnologia* (PTDC/SAU-SER/28806/2017) and under the project UIDB/04501/2020.

2.1 Ethical considerations

Ethical approval was obtained prior to study commencement from the *Unidade de Investigação em Ciências da Saúde: Enfermagem* (UICISA: E) of the *Escola Superior de Enfermagem de Coimbra*, Portugal (NºP517-08/2018), from the Ethics Committee for Health of the *Centro Hospitalar do Baixo Vouga, EPE*, Aveiro, Portugal (N/Ref 0863926) and from the *Hospital Distrital da Figueira da Foz, EPE*, Leiria, Portugal (March 15th 2019) (Annex I). Data protection was ensured by following the European regulation (21). Participants' enrolment and data collection were preceded by a verbal and written description of the study (Appendix I) and written informed consent (Appendix II).

2.2 Study design

An observational descriptive study was conducted (22).

2.3 Sample size

A minimum of fifty participants were aimed to be included in this study since this is the sample size suggested by the COnsensus-based Standards for the selection of health status Measurement INstruments (COSMIN) guidelines to determine measurement properties of measurement instruments with good methodological quality (20, 23).

2.4. Participants

People with ILD were recruited from the *Centro Hospitalar do Baixo Vouga* and *Hospital Distrital da Figueira da Foz*, between January and September 2019. Patients were considered eligible if they had an established diagnosis of ILD (1, 5, 8, 10) and were clinically stable over the past month (i.e., no hospital admissions, exacerbations or changes in medication for the cardiorespiratory system). Patients were excluded if they had other lung diseases (e.g., COPD), signs of cognitive impairment (e.g., dementia), presence of a significant cardiovascular (e.g., unstable cardiac disease), neurological (e.g., neuromuscular dystrophy disease), musculoskeletal disease (e.g., important kyphoscoliosis) or signs of substance abuse (e.g., alcohol) that precluded their participation in data collection or being involved in a community-based PR programme.

Eligible patients were identified by clinicians and contacted by the researcher, who explained the purpose of the study and asked about their willingness to participate. An appointment with the researcher was scheduled with those interested in participating. At this meeting, written information about the study was provided, any remaining doubts were clarified and written informed consent was obtained.

2.5. Data collection

Participants were asked to attend to two assessment sessions, with at least 48-72 hours apart. The initial assessment was performed by one physiotherapist with experience in collecting the outcome measures. Sociodemographic (age, gender, education and occupation) and clinical data (smoking status, medication, long-term oxygen, non-invasive ventilation, number of exacerbations, hospitalisations or emergency admissions in the past year and vital signs) were first obtained, using a structured questionnaire based on the International Classification of Functioning, Disability and Health (ICF) checklist (24). Lung function tests (spirometry and diffusion capacity for carbon monoxide - DL_{CO}) were collected from patients' clinical records. The reduction in DL_{CO} was classified as follows: >60% predicted represents mild severity of lung function, 40-60% predicted moderate severity and <40% predicted severe severity (25).

Comorbidities were assessed and scored according to the Self-Administered Comorbidities Questionnaire (SCQ) (26). This questionnaire has been adapted from the Charlson Comorbidity Index, it is composed of 12 medical and 3 optional conditions and takes approximately 2 minutes to be completed (27). The SCQ attributes a maximum of 3 points to each condition, namely 1 point for the presence of the problem, 1 point if receiving treatment for it and 1 point if the medical condition limits the person activities (26, 27). Scores range from 0 to 45, with higher scores indicating more severe comorbidities (26, 27).

Anthropometric data (i.e., height and weight) were collected using a stadiometer (Seca 285, Hamburg, Germany) and a medical Body Composition Analyzer (mBCA 515, Seca, Hamburg, Germany) to compute body mass index (BMI).

Then participants performed the CST-1 and the 6MWT-1. A resting period of at least 30 minutes between tests was given to allow for recovery of patient's vital signs, fatigue and dyspnoea to their baseline values (a longer period was given, after the 30 min, if patients had not returned to their baselines levels). In the second session, the CST-2 was performed and patient-reported outcome measures (PROMs) were collected, namely the mMRC (28),

CAT (29), SGRQ (30) and FACIT-FS (31). PROMs were collected in the reported standardised order. In one of the sessions, a second-rater was present to assess the CST. After a 12-week community-based PR programme, completed by a subgroup of participants, all PROMs and the CST-3 and 6MWT-2 were repeated.

2.5.1. Patient-reported outcome measures (PROMs)

A brief explanation about the purpose of each measure was first given to participants. PROMs were then applied using a supervised self-administration method.

Modified medical research council questionnaire (mMRC)

The mMRC is a simple questionnaire which measures activities limitation due to dyspnoea. It is a 5-point scale with scores ranging between 0 and 4: 0, no breathlessness except on strenuous exercise; 1, shortness of breath when hurrying or walking up a slight hill; 2, walks slower than people of same age on the level because of breathlessness or has to stop when walking at their own pace on the level; 3, stops for breath after walking 100 meters or after few minutes on the level; and 4, too breathless to leave the house or breathless when dressing or undressing (32). Higher scores indicate greater breathlessness severity on daily activities (32). It takes approximately 1 minute to be completed (28). A Portuguese version of the mMRC can be freely accessed through Direção-Geral da Saúde guideline (33). The mMRC has been used in patients with ILD and it has been shown to be valid, reliable and significantly associated with forced vital capacity (FVC) in patients with IPF (rank correlation coefficient r_s=– 0.75; p=0.0001) (28). Although it is a questionnaire commonly used, namely in COPD, there is no consensus on whether mMRC is or is not a responsive measure to PR (34). Nevertheless, a significant mean difference in mMRC (0.7 points, 95% CI 0.1-1.3) after an 8-week exercise training programme has been reported (35).

COPD assessment test (CAT)

The CAT is an 8-item unidimensional scale developed to assess the impact of COPD and the most burdensome symptoms in patients' life (i.e., cough, sputum, chest tightness, dyspnoea, home daily activities, confidence leaving home, sleep and energy levels) in a 5-point scale (29). Scores range from 0 to 40 and are interpreted as follows: 5 represents the upper limit of normality in healthy non-smokers; <10 represents low impact, 10-20 medium, 21-30 high and >30 very high impact of the disease on the patient´s health (36). The CAT takes on average less than 2 minutes to be completed (37). A Portuguese version of the CAT can be freely accessed through the COPD Assessment Test website (36). In patients with ILD, CAT has shown to be a reliable (Cronbach's α coefficient=0.869, and intraclass correlation coefficient, ICC =0.742) and valid measure (correlation with the SGRQ, r=0.723-

0.8, p<0.001)(37, 38). CAT has also been demonstrated to be a responsive measure to PR programme in patients with COPD (ES=0.75) (39). In a group of non-COPD patients, including patients with ILD, changes in CAT after a PR programme were significant, positive and weakly correlated with the different domains of the Chronic Respiratory Questionnaire (r=-0.25 to -0.38, p<0.001 to 0.009) (40).

St. George's respiratory questionnaire (SGRQ)

The SGRQ is a comprehensive well-established and self-administered questionnaire to assess health-related quality of life (30). The SGRQ integrates three domains: symptoms (frequency and severity), activities (influence of breathlessness on mobility or physical activity) and impact (psychosocial impact of the disease), with a 3-month period recall for symptoms and a current state recall for the other 2 components (30). It has 50 items scored on a 5-point Likert scale or a dichotomous form. The whole questionnaire takes approximately 10 minutes to be completed (41). A Portuguese version of the SGRQ has been developed by the study group at St George's, University of London and can be freely requested through their website (42). The SGRQ total score is given by a combination of the three-domain scores, ranging from 0 (no impairment) to 100 (worst possible health status)(43). Although it was developed originally for patients with COPD and asthma, it has been used in patients with ILD (43-45) and excellent internal consistency (Cronbach's α coefficients=0.75-0.91) and intra-rater reliability (ICC=0.66-0.77) was reported (43). The responsiveness of the SGRQ has been little explored in people with ILD. Excellent responsiveness to PR has been shown in COPD (ES=0.87) (39), whereas in other chronic lung diseases, including a small percentage of patients with ILD, all domains and total score of the SGRQ have revealed a significant, but small responsiveness to PR (standardized response mean=0.33-0.51) (46).

Functional assessment of chronic illness therapy – fatigue scale (FACIT-FS)

The FACIT-FS is a multi-dimensional 13-item questionnaire that assesses tiredness, weakness and difficulty in handling daily living activities due to fatigue, over the previous 7 days (31). Each item has a 5-points Likert scale, ranging from 0 (not at all) to 4 (very much). The total score ranges from 0 to 52, with higher scores indicating less fatigue. The average time needed to complete the FACIT-FS is 5 to 10 minutes (31). A Portuguese version of the FACIT-FS has been developed by the FACIT study group and it can be freely accessed through their website (47). The FACIT-FS has been used in some studies to assess fatigue in patients with ILD (48, 49). It has shown a significant, positive and strong correlation with health-related quality of life, namely with the two quantified components of the EuroQol-5Domain health questionnaire (r_s=0.78 and 0.77) (49). A cut-off lower than 43 is commonly

used to interpret presence of clinically relevant fatigue (50). No studies were found, regarding the responsiveness of this measure to PR in patients with ILD.

2.5.2. Chester Step Test

The CST was performed using a digital recording with timed metronome rhythms and a 20 cm tall single-step device, according to CST general guidelines (19). The CST has 5 stages, each of 2 minutes duration. The timed metronome set the step cadence, which starts at 15 steps/minute and increases 5 steps/minute every 2 minutes: stage 1 (15 steps/minute); stage 2 (20 steps/minute); stage 3 (25 steps/minute); stage 4 (30 steps/minute); stage 5 (35 steps/minute). The maximum test duration is 10 minutes, corresponding to the final stage 5. Heart rate (HR) was recorded every minute, with a bracelet connected to a cardio frequency meter (Kinetik Medical Devices Lta. NG90 6B, UK) placed on the participants' chest. The perceived dyspnoea and fatigue and blood oxygen saturation (SpO_2) were recorded at the end of each 2-minute stage, with the modified Borg Scale and a pulse oximetry (Konica Minolta, Pulsox-300i, Japan), respectively (51). The CST ended when the participant reached 80% of the reserve HR, using the Karvonen equation (51), if the SpO_2 dropped below 85% or if the participant was unable to maintain the step cadence for 15 seconds. If 80% of the reserve HR was reached at mid-stage, providing there were no signs of distress or discomfort, the test was normally continued to the end of the 1-minute stage, as recommended (51). Moreover, if the participant showed signs of being over-tired, breathless or dizzy, the CST was immediately terminated. The main outcome measure of the CST was the total number of steps taken. The best CST, where the patient performed the highest number of steps, was selected for validity analysis.

2.5.4. 6-Minute Walk Test

The 6MWT is a reliable (ICC=0.82-0.96), valid (positive and strong correlation with maximum oxygen uptake, r=0.78, $p<0.0001$) and responsive (weak correlations with measures of physiological function, dyspnoea and SGRQ, r=-0.231 to 0.270, $p<0.001$; mean difference ranging from 25.1 to 46.3 meters, $p<0.05$), measure of exercise tolerance in patients with ILD (17, 52-54). The 6MWT was performed on a flat, straight, 30 meters length corridor with a hard surface, according to the European Respiratory Society/American Thoracic Society guidelines (55). Before each 6MWT, participants rested on a chair, located near to the starting position, for at least 10 minutes. Then, participants were instructed to walk as fast as possible, without running or jogging, for 6 minutes (55). If participants requested to pause during the test or their SpO_2 dropped below 85%, they were allowed to sit on the chairs placed along the corridor (55). The number of pauses and

motives to pause were registered. Participants were encouraged to resume walking as soon as they could or when their SpO_2 reached at least 88%. Criteria for immediately terminating the test included chest pain, intolerable dyspnoea, leg cramps, staggering, diaphoresis and pale or ashen appearance (55). Standard encouragement was given each minute (55). The 6MWD was the main outcome measure.

2.6 Intervention

All participants were given the opportunity to participate in a community-based PR programme, conducted at the Respiratory Research and Rehabilitation Laboratory (Lab3R) of the School of Health Sciences, University of Aveiro. The PR programme lasted 12 weeks and included exercise training sessions, a component of education and psychosocial support and recommendations for exercise and physical activity at home (5, 13, 56). Exercise training sessions were performed twice a week, each session had an approximate duration of 60 minutes, and was delivered by an experienced physiotherapist following the international guidelines (13). It included a warm-up period, aerobic training, strength training and a period of calming down (56). Furthermore, an additional component of balance training and inspiratory muscle training was introduced for patients with balance deficits or inspiratory muscle weakness (13, 56). Balance and inspiratory muscle strength were assessed secondarily with brief-balance evaluation systems test (Brief-BESTest) and respiratory pressure meter (MicroRPM, CareFusion, Kent, United Kingdom), respectively (56-60). A cut-off value of 16.5 points in Brief-BESTest and $-80cmH_2O$ for men and $-70cmH_2O$ for women in inspiratory muscle strength were used to determine those with impairments (58, 59). HR, SpO_2, perceived dyspnoea and fatigue, measured with the modified Borg scale (61), were monitored throughout the sessions. The intensity of the aerobic and strength training were individually prescribed using the 6MWT (62) and the one-repetition maximum (1-RM) method (13). During the PR programme, progression in the training intensity was tailored according to the rate of perceived exertion, dyspnoea and fatigue (i.e., 4-6 in the modified Borg scale) (56). A detailed description of the exercise training protocol can be found in Table 1.

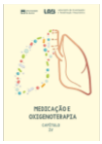
Table 1: Community-based pulmonary rehabilitation programme – exercise training component.

Exercise Type	Modality	Intensity	Duration	Examples
Warm-up	Global range of motion exercises; breathing control	Low	5 min	 
Aerobic training	Walking; cycling; stepping	80% of the 6MWT mean walk velocity 60 – 80% of W_{peak} 60 – 80% of HR_{max}	20 – 30 min	 
Resistance training	Free weights and elastic bands (major muscle groups of upper and lower limbs and trunk)	60 – 70% of 1-RM	20-25 min (8 exercises, 2 sets of 10 – 12 repetitions)	 
Balance training	Upright positions; adjustments of the centre of gravity in static and dynamic postures; dual cognitive and motor task	N/A	10 min	 
Cool-down	Breathing control; stretching exercises; relaxation therapy	Low	5 min	 

Legend: 6MWT, 6-minute walk test; Wpeak, work peak; HRmax,maximum heart rate; 1-RM, one-repetition maximum. Adapted from Marques et al. Improving access to community-based pulmonary rehabilitation: 3R protocol for real-world settings with cost-benefit analysis. BMC public health. 2019;19(1):676

Six education and psychosocial support sessions were conducted once every other week by a multidisciplinary team, with a mean duration of 90 minutes (56, 63, 64). Patients' relatives and friends were invited to participate in these sessions (64). A detailed description of the education and psychosocial support component can be found in Table 2.

Table 2: Community-based pulmonary rehabilitation – education and psychosocial support component.

Sessions	Themes	Professional	Flyers
1	Information about Chronic Lung Diseases/ impact on family life Role of pulmonary rehabilitation	General practitioner, nurse and physiotherapist	
2	Role of the domestic environment on respiratory health	Physiotherapist and biologist	
3	Healthy lifestyles: physical activity; action plan Community resources	Physiotherapist and social worker	
4	Management of respiratory symptoms Management and prevention of exacerbations	Physiotherapist and general practitioner	
5	Medication and oxygen therapy	Nurse and general practitioner	
6	Healthy lifestyles: nutrition and sleep Management of stress and anxiety	Nurse, psychologist and nutritionist	

Notes: Flyers available at http://3r.web.ua.pt/(63). Adapted from Marques et al. Improving access to community-based pulmonary rehabilitation: 3R protocol for real-world settings with cost-benefit analysis. BMC public health. 2019;19(1):676

2.7 Data analysis

Data analysis was performed using IBM SPSS Statistics (version 25.0, IBM Corporation, Armonk, NY, USA).

Descriptive statistics, i.e., relative frequencies (percentage), mean ± standard deviation (SD) or median [interquartile range] were used to describe the sample. The Kolmogorov-Smirnov test (KS) was used to determine the normality of data distribution and select the preferable test (65). Outliers were identified, through the inspection of extreme points on the plotted graphs of the variables in study and analysis were performed with and without their presence. We decided not to remove outliers since their presence did not affect results significantly. Tests with a p<0.05 were considered statistically significant. Analysis of reliability, validity, responsiveness and learning effect is presented below (23).

2.7.1. Reliability

Reliability refers to the consistency of a measure or absence of measurement error and its ability to replicate the score from one assessment or rater to another (66). There are two types of reliability, i.e. relative and absolute reliability.

Relative reliability refers to the extent to which individuals maintain their position in a sample over repeated measurements and it was measured using intraclass correlation coefficient (ICC)(66). $ICC_{1,1}$ and $ICC_{2,1}$ models were used to determine intra-rater and inter-rater reliability (67), respectively, according to the following equations:

$ICC_{1,1} = \frac{BMS - WMS}{BMS + (k-1)WMS}$ (equation 1),

$ICC_{2,1} = \frac{BMS - EMS}{BMS + (k-1)EMS + \frac{k}{n}(RMS - EMS)}$ (equation 2),

where BMS is between-subjects mean squares, WMS is within-subjects mean squares, EMS is the error (residual) of mean squares, RMS is between raters mean squares, k is the number of measurements/raters (k=1) and n is the number of participants. An ICC lower than 0.50 was considered of poor reliability, 0.5-0.75 moderate, 0.75-0.90 good and greater than 0.9 excellent reliability (20, 66).

Absolute reliability is the degree to which repeated measurements vary for individuals and it was determined by calculating the standard error of measurement (SEM) and the minimal detectable change at 95% confidence interval (MDC_{95})(66). The SEM was measured according to the following equation: $\mathrm{SEM} = \mathrm{SD}_{difference}/\sqrt{2})$, where $SD_{difference}$ is the SD of

the differences between the CST-1 and CST-2 (20, 68). The MDC_{95} was calculated as follows: $\mathrm{MDC}_{95} = 1.96 \times \sqrt{2} \times \mathrm{SEM}$ (20). The values of SEM and MDC_{95} were also expressed as a percentage of the mean to allow for comparisons and calculated as follow: $\mathrm{SEM}\% = (\mathrm{SEM}/\mathrm{mean}) \times 100$ and $\mathrm{MDC}_{95}\% = (\mathrm{MDC}_{95}/\mathrm{mean}) \times 100$, where mean is the mean of the number of steps taken in CST-1 and CST-2. A MDC_{95}% of less than 30% was considered acceptable (58).

The Bland&Altman method was also applied (20, 23). First, we plotted the difference between the number of steps taken in CST-1 and CST-2 against the mean of the number of steps taken in CST-1 and CST-2 (69). Then, we calculated the mean and SD of the differences between CST-1 and CST-2, the closer the mean difference is to zero and the smaller the SD of the differences, the more reliable is the measure (69). Finally, we calculated the 95% limits of agreement (LoA_{95}) as follows: $\mathrm{LoA}_{95} = \mathrm{mean}_{\,\mathrm{difference}} \pm 1.96 \times \mathrm{SD}_{\mathrm{differences}}$ (69).

2.7.2. Validity

Validity is commonly defined as the extent to which the test can measure the concept it was designed to measure, i.e., if it relates to the gold standard measure (criterion validity) or other measures that assess the same construct (construct validity). Construct validity was assessed by analysing the relationship between the number of steps taken in the best CST and the 6MWD using the Pearson (r) or Spearman (r_s) correlation coefficient, depending on whether the normal distribution of the variables was verified or not, respectively (20). A correlation of 0-0.3 was considered poor, 0.3-0.5 weak, 0.5-0.7 moderate, 0.7-0.9 strong, and 0.9-1.0 excellent (20, 65).

2.7.3. Responsiveness

Responsiveness refers to the ability of an instrument to detect change over time in the construct to be measured (20). Responsiveness was established using three different methods and only participants who attended to at least 65% of PR sessions were included in this analysis (56):

(1) calculating ES using one of the following equations:

ES=$M_A - M_B/\sigma$ (equation 3),

where M_A is the mean of the number of steps taken in CST-3, M_B is the number of steps taken in CST-1 and σ is the SD for the sample,

or ES=$Z/\sqrt{N}$ (equation 4),

where Z is the statistic Wilcoxon T-test and N is the number of total match pairs (18, 70). An ES of >0.5 as considered large, >0.3 medium and >0.1 small (70);

(2) exploring differences between the number of steps taken in the CST-1 and the CST-3 using either paired student´s t-test or non-parametric Wilcoxon T-test, and calculating the mean difference between the post-PR and pre-PR values of the CST (18);

(3) calculating Pearson or Spearman correlation coefficient to analyse the relationships between change in CST-1 and CST-3 with changes in 6MWD, mMRC, CAT, SGRQ and FACIT-FS after completing the 12-week PR programme (23). A correlation of 0-0.3 is considered poor, 0.3-0.5 weak, 0.5-0.7 moderate, 0.7-0.9 strong, and 0.9-1.0 excellent (65).

2.7.4. Learning effect

The learning effect was explored using paired student´s t-test or non-parametric Wilcoxon T-test between CST-1 and CST-2 (71, 72).

3. Results

3.1 Sample characterisation

Seventy-eight patients with ILD were screened to be included in the study. Sixty-six patients were eligible to participate and twelve patients were excluded due to: declined to participate (n=4), dropped-out for no reason given (n=1), presence of a significant cardiovascular disease (n=4), presence of a significant musculoskeletal disease (n=2), signs of cognitive impairment (n=1). Sixty-six patients were included to assess validity. To assess reliability and learning effect only fifty-three patients were included since thirteen individuals did not attend the second assessment session. Forty participants were willing to participate in the 12-week PR programme, but only thirty-three completed the programme and were included to assess the responsiveness of the CST. Reasons for non-completion were non-respiratory complications (n=3), respiratory complications (n=2) and no reason given (n=2). A flow diagram of the recruited and eligible sample is provided in Figure 1.

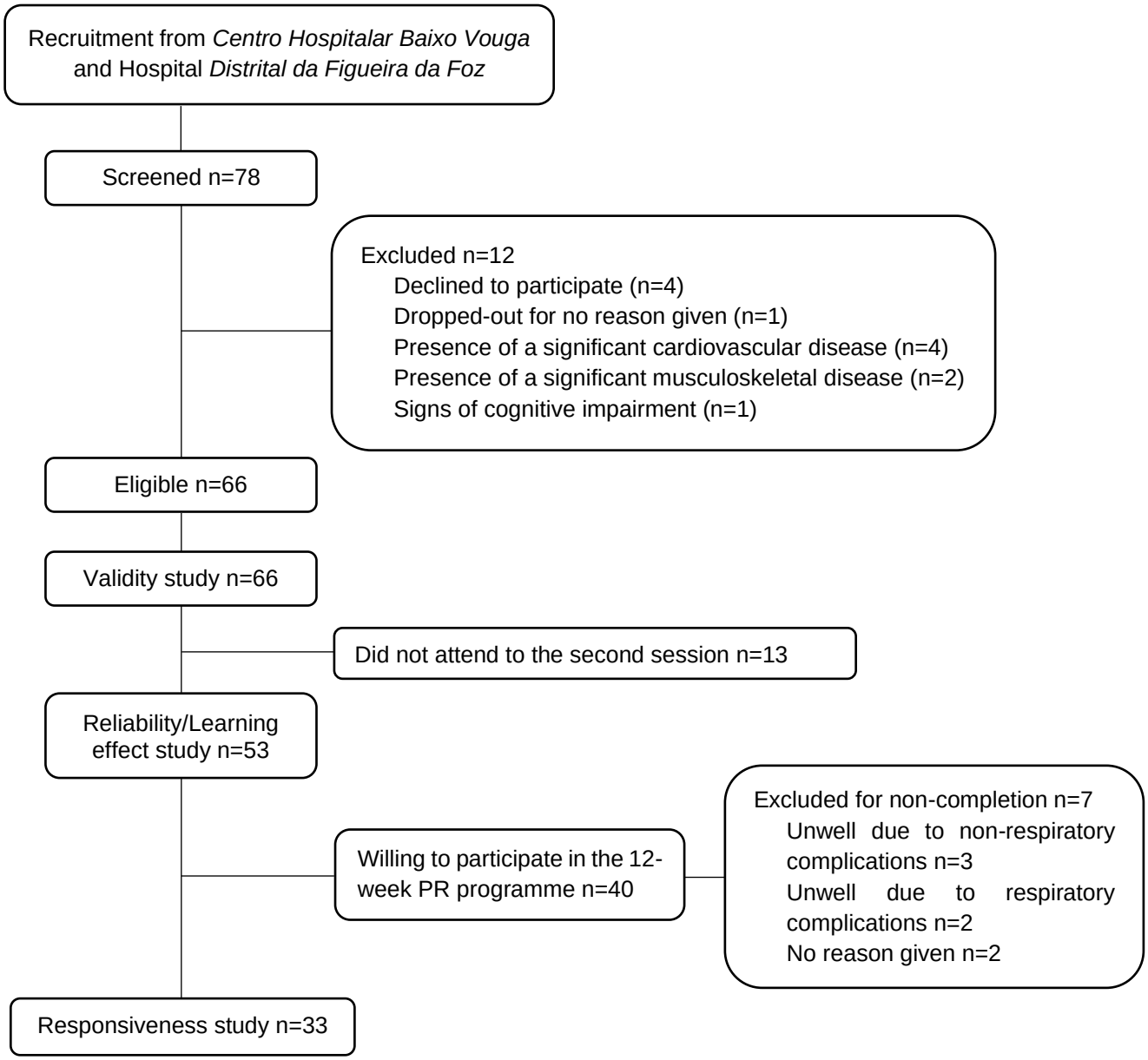


Figure 1: Flow diagram of participants with interstitial lung disease included in the study.

Eligible participants were on average 65.5±12.9 years old, 48.5% male (n=32), with a mean BMI of 28.9±5.2kg/m^2. Approximately half of the sample had completed four years of education (n=35; 53%), most were retired (n=47; 71.2%) and 36.4% were former smokers (n=24). Participants presented a mean forced expiratory volume in one second (FEV_1) of 81.9±19.9% predicted. Nineteen participants (28.8%) presented a mild ILD (DL_{CO} >60%predicted), 18 participants (27.3%) a moderate ILD (40%≤DL_{CO}≤60%predicted), 19 participants (28.8%) a severe ILD (DL_{CO}<40%predicted) and for 10 patients (15.1%) we were unable to access these values. Thirty-one participants used long-term oxygen therapy (47%) and only 5 participants used non-invasive ventilation (7.6%). Regarding the

pharmacological treatment for ILD, 65.2% of participants were treated with glucocorticoid drugs (n=43), 45.5% with immunosuppressant agents (n=30) and 7.6% with antifibrotic drugs (n=5). Most prevalent types of ILD were chronic hypersensitivity pneumonitis (n=29, 43.9%), followed by IPF (n=16, 24.2%) and sarcoidosis (n=6, 9.1%). The average score of the SCQ was 9±3.9. The mean number of steps taken in CST-1, CST-2 and CST-3 were 77.7±50.2, 82.4±55.7 and 99.1±65.3, respectively. The mean 6MWD was 399.4±128.2 meters. Participants presented a mean mMRC score of 2 [1-2] points, a mean CAT score of 12.4±7.1 points, a mean SGRQ total score of 40.3±18.5 points and a mean FACIT-FS score of 39.2±7.8 points. Sample characterisation is summarized in Table 3.

Table 3: Sample characterisation (n=66)

Characteristics	**Eligible participants (n=66)**
Age, years	65.5±12.9
Gender, male n (%)	32 (48.5)
BMI, kg/m^2	28.9±5.2
Years of education, n (%)	
Illiterate	1 (1.5)
1-4	35 (53)
5-9	14 (21.2)
10-12	9 (13.6)
University	7 (10.6)
Current occupation, n (%)	
Employed	9 (13.6)
Housekeeper	4 (6.1)
Retired	47 (71.2)
Unemployed	5 (7.6)
Other	1 (1.5)
Smoking status, n (%)	
Current	2 (3)
Former	24 (36.4)
Never	42 (63.6)
Packs/year	35.0 [7.0-55.8]
Exacerbations/year, n (%)	
0	48 (72.7)
1	14 (21.2)
≥2	4 (6)
Lung function	
FEV_1,	2.1±0.7
FEV_1, %predicted	83.7±20.8
FVC, L	2.5±0.8
FVC, %predicted	79.4±18.8
FEV_1/FVC, %	82.7±9.2
DL_{CO}, %predicted	49.0±18.3
DL_{CO} >60%predicted, n (%)	19 (28.8)
40%≤DL_{CO} ≤60%predicted, n (%)	18 (27.3)
DL_{CO} <40%predicted, n (%)	19 (28.8)

Long-term oxygen therapy, n (%)	31 (47)
Non-invasive ventilation, n (%)	5 (7.6)
Pharmacological treatment for ILD, n (%)	
Glucocorticoids	43 (65.2)
Immunosuppressant	30 (45.5)
Antifibrotics	5 (7.6)
ILD types, n (%)	
IPF	16 (24.2)
Sarcoidosis	6 (9.1)
Chronic hypersensitivity pneumonitis	29 (43.9)
NSIP secondary to systemic sclerosis	2 (3)
UIP secondary to systemic sclerosis	4 (6.1)
UIP secondary to rheumatoid arthritis	2 (3)
Anti-synthetase syndrome	2 (3)
Desquamative interstitial pneumonia	1 (1.5)
Lymphocytic interstitial pneumonia	1 (1.5)
Silicosis	1 (1.5)
Respiratory bronchiolitis ILD	1 (1.5)
Follicular bronchiolitis Sjogren's syndrome	1 (1.5)
SCQ	9±3.9
CST-1	77.7±50.2
CST-2	82.4±55.7
CST-3	99.1±65.3
6MWT	399.4±128.2
6MWT, %predicted	83.1±26.4
mMRC	2 [1-2]
CAT	12.4±7.1
SGRQ (Total score)	40.3±18.5
FACIT-FS	39.2±7.8

Notes: Values are presented as mean±standard deviation or median [interquartile range].

Legend: BMI, body mass index; CST, Chester step test; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; DL_{CO}, diffusion capacity for carbon monoxide; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; NSIP, non-specific interstitial pneumonia; UIP, usual interstitial pneumonia; SCQ, self-administered comorbidities questionnaire; 6MWT, 6-minute walk test; mMRC, modified Medical Research Council questionnaire; CAT, COPD assessment test; SGRQ, St George's respiratory questionnaire; FACIT-FS, functional assessment of chronic illness therapy – fatigue scale.

3.2 Reliability

The CST demonstrated excellent relative reliability, for both intra-rater reliability ($ICC_{1,1}$=0.95; 95%CI 0.91-0.97) and inter-rater reliability ($ICC_{2,1}$=1.0; 95%CI 0.99-1.0). Regarding absolute reliability, SEM and MDC_{95} were calculated and their values were 11.8 steps (SEM%=14.7%) and 32.6 steps (MDC_{95}%=40.7%), respectively. The Bland&Altman plot was created and a mean difference of -4.72 steps was observed with the LoA95 ranging from -37.28 and 27.84 steps (Figure 2).

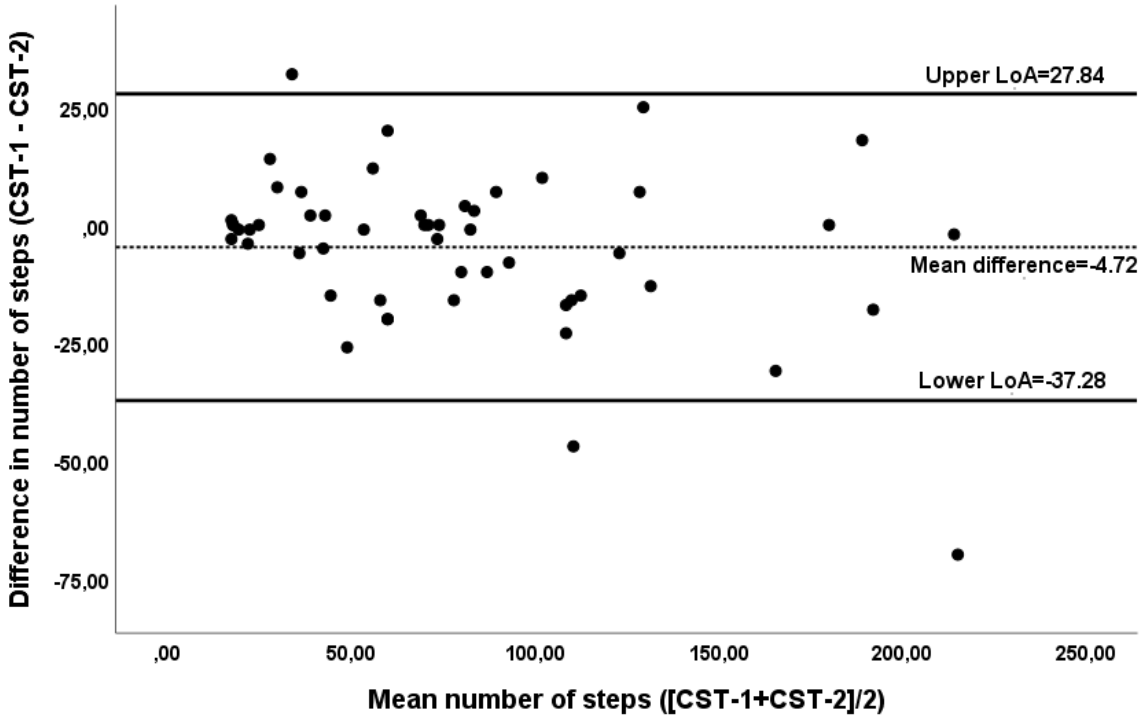


Figure 2: Bland and Altman plot of the difference between number of steps in the Chester step test-1 and the Chester step test -2 against the mean of the number of steps in the Chester step test -1 and the Chester step test -2. The dashed horizontal line represents the mean difference, and the solid horizontal lines represent the 95% upper and lower limit of agreement.

3.3 Validity

Only the 6MWD presented normal distribution, therefore, the Spearman correlation coefficient was used. The correlation between the number of steps of the best CST and the 6MWD was significant, positive and strong (r_s=0.85, p=0.00).

3.4 Responsiveness

Variables of the CST were not normally distributed, therefore the non-parametric formulas were used to calculate the ES (equation 4), to explore differences between CST-1 and CST-3 and for correlation analysis. The ES was moderate (ES=0.49) and differences between the number of steps taken in the CST-1 (pre-PR) and the CST-3 (post-PR) were statistically significant (p=0.004). Mean difference was 12.6±30.7 steps (95%CI 1.8-23.5). The Spearman correlation coefficient was applied and the correlation between change in CST and change in 6MWD, CAT and SGRQ were not significant (Table 4). Changes in the CST were significant, negative and weak (r_s=-0.37, p=0.036) correlated with change in the mMRC and significant, positive and moderately (r_s=0.60, p=0.0001) correlated with change in FACIT-FS (Table 4).

Table 4: Correlations between changes in the Chester step test and changes in the 6-minute walk test, the modified Medical Research Council questionnaire, the COPD assessment test, the St. George's respiratory questionnaire and the functional assessment of chronic illness therapy – fatigue scale.

		Change in 6MWD	Change in mMRC	Change in CAT	Change in SGRQ	Change in FACIT-FS
Change in CST	*Spearman coefficient*	0.28	-0.37*	-0.15	-0.14	0.60*
	p	0.122	0.036	0.407	0.436	0.000

Notes: correlations were calculated using Spearman correlation coefficient; *p<0.05.
Legend: CST, Chester step test; 6MWT, 6-minute walk test; mMRC, modified Medical Research Council questionnaire; CAT, COPD assessment test; SGRQ, St George's respiratory questionnaire; FACIT-FS, functional assessment of chronic illness therapy – fatigue scale.

3.4 Learning effect

Participants who attended both assessment sessions and performed CST-1 and CST-2 before integrating the PR programme were included for learning effect analysis (n=53). Since CST-2 did not present normal distribution, non-parametric Wilcoxon T-test was used. The mean number of steps taken in CST-1 and CST-2 were 77.7±50.2 and 82.4±55.7, respectively. There was no significant difference between the number of steps taken in the CST-1 and CST-2 (p=0.055).

4. Discussion

This study showed that the CST seems to be a reliable, valid and responsive test with no learning effect, therefore suitable to be used in the assessment of patients with ILD.

Assessment of exercise capacity in all settings (inpatient, outpatient and home) is of paramount importance as exercise intolerance in patients with ILD has been associated with a more reserved prognostic and a poorer health-related quality of life (1, 13). Clinicians and researchers have now at their disposal a field test that is valid and reliable, but also responsive to PR, which is the most effective non-pharmacologic strategy to manage and improve patients' symptoms (3, 13).

Excellent intra-rater and inter-rater reliability were found for the CST. A similar study, which focused on people with COPD and assessed the reliability of the CST also showed excellent relative reliability (ICC of 0.99; 95%CI 0.97-0.99) (16). This finding indicates that CST provides consistent results and excellent agreement between healthcare professionals, which allows for comparisons of the patients´ results even when CST is applied by different raters and on different occasions, i.e., pre and post PR programme (73). Moreover, it also suggests that only minimal training is required for healthcare professionals to apply CST.

Our findings suggest that it is necessary to improve above 32.6 steps to assume that a statistical change in patients' performance was achieved (20). Although this cut-off is informative, MDC_{95} values do not determine whether that change is clinically meaningful or not. Therefore, future studies should aim to determine the minimal clinically important differences (MCID) of the CST in patients with ILD, using both anchor (i.e., mean change, the receiver operating characteristic curves and linear regression analysis) and distribution-based methods (i.e., 0.5 times the SD, SEM, 1.96 times the SEM; MDC_{95} and ES) (17). The MDC_{95}% of our study was also above the 30% acceptable limit (58). It is likely that this finding was influenced by the high heterogeneity of symptoms and exercise capacity observed in our sample of patients within disease subgroups (DL_{CO}>60%predicted 28.8%; 40%≤DL_{CO}≤60%predicted 27.3%; DL_{CO}<40%predicted 28.8%), thus increasing the MDC_{95} value (1, 74).

In the present study, no evidence of systematic bias was observed. In patients with COPD, the CST showed smaller and narrower values of mean difference and LoA95 (mean difference of -1.1 steps with LoA95 ranging from -20.2 to 17.9 steps)(16). It is likely that the high heterogeneity observed in our sample of patients within disease subgroups may have contributed to the wider range of the LoA95, especially those patients that achieved higher stages on the CST.

Regarding construct validity, the CST revealed a strong correlation with the 6MWT. Similar results were found for ISWT in the same population (r=0.76, p<0.0001), while a lower correlation was observed between the number of steps achieved in the CST and the 6MWD in patients with COPD (r=0.60, p=0.001) (16, 18). In comparison with the 6MWT and the ISWT, the CST has some advantages since it is a functional test that can be applied in a reduced physical space. As reported previously, the 6MWT requires a 30 meters length corridor, and the ISWT a 10 meters corridor, which is often difficult to find in home settings and in some hospitals and clinics (75). Our results indicate that the CST is a valid test to assess exercise tolerance in patients with ILD, thus it may be an alternative to other more demanding field walking tests.

The ES was found to be medium and the mean difference of the CST was 13 steps, approximately. One study that used the ES to evaluate the responsiveness of the ISWT to PR in patients with ILD showed a large ES (0.85) (18). Another study that assessed responsiveness of the 6-minute step test (6MST) in patients with COPD revealed a mean difference of 11 steps after a 6-week physical training programme (3 session/week).

Although there are several distinct features among the studies (CST: externally-paced vs. 6MST: self-paced, physiological mechanisms of exercise limitation in patients with ILD vs. COPD and PR programme vs. physical training programme), the mean change of steps was similar (76). Finally, correlations between change in the CST were only observed with changes in mMRC and FACIT-FS, which indicates that improvements in exercise capacity are related to significant improvements in dyspnoea and fatigue symptoms. Significant improvements in mean differences in mMRC and in the dyspnoea and fatigue categories of the Chronic Respiratory Disease Questionnaire have been previously reported after exercise training in patients with ILD (35). Initially, we hypothesized a significant, negative and weak correlation between change in the CST and change in the 6MWT, the CAT and the SGRQ, since several studies indicated that they are weak responsive measures to PR (17, 35, 40, 46, 77, 78). However, in those studies, the authors did not use correlations between change in CAT/SGRQ and change in an outcome measure of exercise capacity to assess their responsiveness to PR. As stated previously, our sample presented high heterogeneity with variable disease progression, which may have had a negative impact on the expected correlations between change in the CST and the 6MWT (1, 74). Another possible explanation is that the sample size used in this analysis (n=33) was below the sample size suggested by COSMIN guidelines (n=50) (20, 23). Further studies, with larger sample sizes are needed to draw stronger conclusions regarding the responsiveness of the CST.

Lastly, our results showed that there were no statistically significant differences between the CST-1 and the CST-2. This finding suggests that the CST has no learning effect, therefore a familiarization test may not be needed to accurately assess exercise capacity in patients with ILD. This is a significant advantage over the 6MWT and ISWT in terms of time consumption (62). However, this interpretation should be done with caution given that statistical significance was close to 0.05 thus, confirmation of this finding is recommended with a larger sample.

4.1 Strengths and limitations

There are some strengths and limitations of the present study that need to be acknowledged. An important strength is that we assessed the main measurement properties of an instrument to assess exercise capacity possible to be used in any setting, including those with physical space constrains. Moreover, the methodology and sample size used were defined following COSMIN guidelines, which provides general principles that

should be taken into account in the design of all studies on measurement properties (20, 23).

However, some limitations came across during this study. First, we only had the opportunity to assess construct validity, therefore we only relate the CST to another measure that theoretically assesses the same construct to be measured (6MWT) and not the gold standard (CPET). Second, we could not evaluate the effects of disease severity and variability on the MDC_{95} and on the response to PR since our sample size was too small to perform subgroup analysis. Third, our study only included patients with clinical stable ILD and those patients that had exacerbations during the PR programme had to be excluded since they were unable to continue or return to the programme. For this reason, our results cannot be generalised to those with exacerbated disease.

4.2 Future work

Future studies should address criterion validity, by correlating the number of steps taken in the CST with $VO_{2\ peak}$ achieved in the CPET. Additionally, more studies with larger sample sizes including patients with different ILD types and disease severities should review the measurement proprieties of the CST and calculate their MCID. Finally, studies should review DL_{CO} cut-off points that determine the severity of ILD in order to better characterise patients and reduce the variability observed within disease subgroups.

5. Conclusions

The CST seems to be a reliable, valid and responsive test to evaluate exercise tolerance in patients with clinical stable ILD. Due to its characteristics, the CST may constitute an appropriate alternative to 6MWT and ISWT since it requires even less space to be applied than those field walk tests and does not require a familiarization test.

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Annex I – Ethics approval

COMISSÃO DE ÉTICA

da **Unidade Investigação em Ciências da Saúde: Enfermagem** (UICISA: E)

da **Escola Superior de Enfermagem de Coimbra** (ESEnfC)

Parecer Nº P517-08/2018

Título do Projecto: Reabilitação respiratória e microbiota nas exacerbações da doença pulmonar obstrutiva crónica (DPOC) - PRIME

Identificação das Proponentes

Nome(s): Alda Sofia Pires de Dias Marques

Filiação Institucional: Universidade de Aveiro

Investigador Responsável/Orientador: Alda Sofia Pires de Dias Marques

Relator: Maria Filomena Botelho

Parecer

O projecto tem como objectivos gerais estabelecer o papel da microbiota das vias aéreas, inflamatórios e clínicos na predição das exacerbações agudas da DPOC assim como aumentar a evidência da reabilitação respiratória nas exacerbações agudas da DPOC. Como objectivos específicos pretende: 1) explorar as alterações longitudinais clínicas da microbiota e da inflamação entre períodos estáveis e exacerbados; 2) estabelecer a viabilidade e efeitos a curto e a longo prazo da reabilitação respiratória na comunidade em fase estável e durante as exacerbações agudas da DPOC e comparar os seus efeitos com os obtidos no meio hospitalar; 3) definir as características dos doentes que irão beneficiar mais da reabilitação respiratória na comunidade.

Segundo os autores o estudo é quasi-esperimental, e a amostra será constituída por 156 doentes com DPOC, recrutados em Instituições Hospitalares (Centro Hospitalar do Médio-Ave, Centro Hospitalar Entre Douro e Vouga, UL5 Matosinhos, Centro Hospitalar do Baixo Vouga, ULS Guarda, Hospital Distrital da Figueira da Foz), em Instituições de Cuidados Primários (ARS Norte e ARS Centro) e Domicílios.

Os critérios de inclusão e de exclusão estão claramente definidos. Existe garantia de confidencialidade. São apresentados o consentimento informado e os instrumentos de colheita de dados.

Atendendo ao formato da investigação, a Comissão de Ética dá o seu parecer favorável.
Contudo o presente parecer não dispensa a autorização formal das entidades onde vai decorrer o estudo, nem a submissão às Comissões de Ética das Instituições de onde os doentes são provenientes, caso existam.

O relator: Maria Filomena Botelho

Data: 19/9/2018 O Presidente da Comissão de Ética: Maria Filomena Botelho

UNIDADE DE INVESTIGAÇÃO EM CIÊNCIAS DA SAÚDE

Escola Superior de Enfermagem de Coimbra

FCT

CENTRO HOSPITALAR DO BAIXO VOUGA, E.P.E. / AVEIRO

Avenida Artur Ravara – 3814-501 AVEIRO
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Exma. Senhora
Dra. Alda Marques
Escola Superior de Saúde da Universidade de Aveiro,
Edificio 30
Agras do Castro – Campus Universitário de Santiago
3810-193 Aveiro

S/ Ref.ª *S/ Comunicação de* *N/ Ref.ª* 086892 *Aveiro,* 02.10.2013

ASSUNTO: **Resposta ao V/ Pedido de confirmação para a realização de estudo no CHBV, E.P.E.**

Em resposta à s/ solicitação subordinada ao tema "PRIME – Pulmonary Rehabilition Innovation and Micribiota in Exacerbations of COPD" vimos, pelo presente, informar que por deliberação do Conselho de Administração, nesta data, se encontra autorizado o pedido formulado.

Nesse sentido, solicitamos a V. Exa se digne enviar um relatório final ao Serviço de Investigação e Formação do CHBV, E.P.E.

Com os melhores cumprimentos,

A Diretora do Serviço de Investigação e Formação

Joana Guimarães

(Dra. Joana Guimarães)

Na resposta indicar o número e as referências desde documento. Em cada ofício tratar só de um assunto.

From: hdff <hdff@hdfigueira.min-saude.pt>
Sent: 15 de março de 2019 16:35
To: Alda Marques <amarques@ua.pt>
Cc: M.ª da Conceição Machado Veloso Gomes Morais <conceicaomorais@hdfigueira.min-saude.pt>; Manuel Teixeira Marques Verissimo <mverissimo@hdfigueira.min-saude.pt>; Ana Raquel Farias Correia Santos Andrade <anaraquelsantos@hdfigueira.min-saude.pt>; Maria Susana Ferreira Magalhães <susana.magalhaes@hdfigueira.min-saude.pt>; Enfermeiro Diretor <enf.diretor@hdfigueira.min-saude.pt>; Direção Clinica <dir.clinica@hdfigueira.min-saude.pt>
Subject: Adenda - projeto PRIME "Pulmonary Rehabilition Innovation and Microbiota in Exacerbations of COPD"

Exma. Senhora,

Encarrega-me o Prof. Doutor Manuel Teixeira Veríssimo, Presidente do Conselho de Administração do Hospital Distrital da Figueira da Foz, EPE de informar que o pedido apresentado para adenda ao projeto Prime "Pulmonar Rehabilition Innovation and Microbiota in Exacerbations of COPD foi autorizado em reunião do Conselho de Administração do dia 12 de março de 2019.

Com os meus cumprimentos,

Ana Maria Rodrigues

Secretariado do Conselho de Administração

REPÚBLICA PORTUGUESA
SAÚDE

SNS SERVIÇO NACIONAL DE SAÚDE

HDFF Hospital Distrital da Figueira da Foz, E.P.E.

Hospital Distrital da Figueira da Foz, EPE
Gala - S. Pedro; 3094-001 - Figueira da Foz
Tlf: 233 40 20 51; Fax: 233 431 268

Appendix I – Participant information sheet

Folha de informação ao participante

O Sr./Sr.ª está a ser convidado/a para participar no estudo de investigação clínica intitulado: "Reabilitação respiratória e microbiota nas exacerbações da DPOC – PRIME". Mas, antes de decidir, é importante que compreenda porque é que a investigação está a ser realizada e o que é que a mesma envolve. Por favor, leia a informação com atenção e discuta a sua participação com outros, se assim o entender. Se houver algo que não esteja claro para si ou necessitar de informação adicional, por favor pergunte aos investigadores (contactos no final deste documento). Use o tempo que precisar para decidir se deseja ou não participar.

Muito obrigado desde já por ler a informação.

Qual é o propósito do estudo?

Este estudo visa estabelecer o papel dos dados da microbiota, inflamatórios e clínicos na trajetória das doenças respiratórias e aumentar a evidência da Reabilitação Respiratória.

As doenças respiratórias são atualmente a 3ª e 4ª causa de morte em todo o mundo e impõe uma sobrecarga significativa e crescente a nível individual, e nos sistemas de saúde, económicos e sociais. Estudos recentes demonstraram que a Reabilitação Respiratória, que é composta por treino de exercício físico, educação e apoio psicossocial, é um dos tratamentos mais efetivos para estas situações. No entanto, a maior parte dos programas de Reabilitação Respiratória decorrem em meio hospitalar, estando acessíveis a menos de 1% da população que poderia beneficiar desta intervenção, pelo que são necessários estudos na comunidade, que aproximem esta intervenção dos doentes que podem beneficiar da mesma. Assim, os resultados deste estudo irão contribuir para melhorar o conhecimento sobre as doenças respiratórias e informar sobre as estratégias para prevenir, detetar precocemente e gerir as mesmas. Para que seja possível alcançar estes objetivos vimos então solicitar a sua participação neste estudo que será realizado pela Escola Superior de Saúde da Universidade de Aveiro/iBiMED.

Porque é que fui escolhido?

Foi escolhido/a porque é uma pessoa com doença respiratória em fase estável. Para o estudo, precisamos de dados de aproximadamente 50 pessoas, com uma condição clínica semelhante à sua, que aceitem participar.

Tenho de participar?

A decisão de participar, ou não, é completamente sua. Se decidir participar vai-lhe ser pedido que assine um formulário de consentimento informado mas, é totalmente livre de desistir a qualquer momento, sem que para tal tenha de dar qualquer justificação. A decisão de desistir ou de não participar, não afetará a qualidade dos serviços de saúde ou qualquer outro, que lhe são prestados agora ou no futuro.

O que me acontecerá caso decida participar?

Se decidir participar, após assinar e entregar aos investigadores o consentimento informado, será feita uma avaliação do seu estado de saúde geral. Esta avaliação será realizada em duas ocasiões separadas por 48 a 72 horas. Primeiro, ser-lhe-ão realizadas algumas perguntas acerca do seu estado de saúde geral. Seguidamente, ser-lhe-á medida a sua composição corporal numa balança. Mediremos também a quantidade de oxigénio no seu sangue e a sua frequência cardíaca através de um oxímetro (pequeno aparelho que se coloca no dedo e nos dá a informação em segundos). De seguida avaliaremos a sua frequência respiratória observando a sua região torácica e abdominal e mediremos a tensão arterial com um medidor digital. A avaliação da força dos seus músculos da coxa e braço realizar-se-ão através de um aparelho que se encosta à região do corpo em teste, e em que lhe é pedido que realize o máximo de força que conseguir e, em breves segundos, o aparelho indica a força daquele músculo. Avaliaremos também a sua capacidade funcional através de um

teste de sentar e levantar de uma cadeira, marcha e equilíbrio. Adicionalmente, ser-lhe-á também pedido que coloque um pouco de saliva para um copo (semelhante ao que utiliza quando realiza análises clínicas) para análise. Iremos apurar a sua tolerância ao esforço através de um teste que consiste em subir e descer um degrau ao som de um bip. Por último, ser-lhe-á pedido que responda a questionários breves para avaliar o impacto da doença no seu dia-a-dia. Nenhum dos testes realizados provoca qualquer dor ou desconforto. A duração da avaliação será de aproximadamente 60 minutos, no Laboratório de Investigação e Reabilitação Respiratória (Lab3R) da Escola Superior de Saúde da Universidade de Aveiro.

Se o médico que o acompanha assim o entender, e caso seja da sua concordância, poderá também realizar um programa de Reabilitação Respiratória, no sentido de melhorar o seu estado de saúde e ter a sua condição monitorizada durante três meses.

Quais são os efeitos secundários, desvantagens e riscos se eu resolver participar?
Não existem efeitos secundários, desvantagens ou riscos de participar no estudo.

Quais são os possíveis benefícios se eu resolver participar?
Toda a informação clínica recolhida será fornecida ao médico que o acompanha e poderá ser-lhe fornecida a si também, caso assim o solicite. Se realizar Reabilitação Respiratória, beneficiará do acompanhamento semanal do seu estado de saúde prestado por um fisioterapeuta especializado na área respiratória e do apoio de uma equipa multidisciplinar. Para além disso, a informação obtida neste estudo, através da sua participação, poderá ajudar a melhorar o conhecimento sobre a origem e desenvolvimento das doenças respiratórias, a sua prevenção, diagnóstico e tratamento.

A minha participação será confidencial?
Toda a informação recolhida no decurso do estudo será mantida confidencial, assegurando o anonimato. Os dados recolhidos serão salvaguardados com um código e palavra-passe, para que ninguém o/a possa identificar. Apenas os investigadores do projeto terão acesso aos seus dados.

O que acontecerá aos resultados do estudo?
Os resultados do estudo serão analisados e incorporados em Dissertações de Mestrado e Teses de Doutoramento e alguns serão publicados em Jornais Científicos. No entanto, em nenhum momento o Sr./Sra. será identificado/a. Se gostar de obter uma cópia de qualquer relatório ou publicação, por favor diga ao investigador.

Quem é que está a organizar e a financiar o estudo?
Este estudo foi suportado pelos orçamentos do Programa Operacional Competitividade e Internacionalização, na sua componente FEDER (POCI-01-0145-FEDER-028806), e da Fundação par a Ciência e a Tecnologia (PTDC/SAL-SER/28806/2017), na sua componente de Orçamento de Estado.

Contactos para mais informações sobre o estudo
Alda Marques (Investigadora Responsável)
Escola Superior de Saúde da Universidade de Aveiro,
Telefone 234 372 462
e-*mail: amarques@ua.pt*

Appendix II – Informed consent

CONSENTIMENTO INFORMADO, LIVRE E ESCLARECIDO PARA PARTICIPAÇÃO EM INVESTIGAÇÃO

de acordo com a Declaração de Helsínquia[1], a Convenção de Oviedo[2] e Regulamento Geral de Proteção de Dados[3]

Por favor, leia com atenção a seguinte informação. Se achar que algo está incorreto ou que não está claro, não hesite em solicitar mais informações. Se concorda com a proposta que lhe foi dirigida, queira por favor assinar este documento.

Título do estudo: Reabilitação respiratória e microbiota nas exacerbações da doença pulmonar obstrutiva crónica (DPOC) – PRIME

Enquadramento: As doenças respiratórias são atualmente a 3ª e 4ª causa de morte em todo o mundo e impõe uma sobrecarga significativa e crescente a nível individual, e nos sistemas de saúde, económicos e sociais (1). Estudos recentes demonstraram que a Reabilitação Respiratória, que é composta por treino de exercício físico, educação e apoio psicossocial, é um dos tratamentos mais efetivos para estas situações. No entanto, a maior parte dos programas de Reabilitação Respiratória decorrem em meio hospitalar, estando acessíveis a menos de 1% da população que poderia beneficiar desta intervenção, pelo que são necessários estudos na comunidade, que aproximem esta intervenção dos doentes que podem beneficiar da mesma (2).

Assim, os resultados deste estudo irão potencialmente contribuir para melhorar o conhecimento sobre as doenças respiratórias e informar sobre as estratégias para prevenir, detetar precocemente e gerir as mesmas. Para que seja possível alcançar estes objetivos vimos então solicitar a sua participação neste estudo que será realizado pela Escola Superior de Saúde da Universidade de Aveiro/iBiMED.

Objetivo do estudo: o PRIME visa estabelecer o papel dos dados da microbiota, inflamatórios e clínicos na trajetória das doenças respiratórias e aumentar a evidência da Reabilitação Respiratória.

Local do estudo e pessoa responsável: Este estudo está a ser realizado pelo Laboratório de Investigação e Reabilitação Respiratória (Lab3R) da Escola Superior de Saúde e pelo Instituto de Biomedicina (iBiMED), Universidade de Aveiro, sob a coordenação científica da Professora Doutora Alda Marques (investigadora responsável), que será também a pessoa responsável por todos os dados adquiridos no âmbito deste projeto.

Explicação do estudo e finalidades: Esta avaliação será realizada em duas ocasiões separadas por 48h a 72h e a recolha de dados consistirá na recolha de alguma informação simples que é relevante para caraterizarmos as pessoas em estudo i) idade, género, habilitações literárias, composição corporal e informação sucinta sobre a sua saúde, e.g., medicação em uso, número de exacerbações e visitas ao hospital no último ano; ii) sinais vitais e saturação periférica de oxigénio; iii) função respiratória; iv) força muscular; v) capacidade funcional; vi) tolerância ao esforço; vii) impacto da sua doença no seu dia-a-dia. Ser-lhe-á também pedido para colocar um pouco de saliva para um copo (semelhante ao que utiliza quando realiza análises clínicas) para posterior análise do seu microbioma e mediadores inflamatórios. Nenhum dos testes realizados provoca qualquer dor ou desconforto. A duração da avaliação será de aproximadamente 60 minutos.

Se o médico que o acompanha assim o entender e caso seja da sua concordância, poderá também realizar um programa de Reabilitação Respiratória, no sentido de melhorar o seu estado de saúde e ter a sua condição monitorizada durante três meses.

Estes dados estão a ser recolhidos para se estudar o papel dos dados clínicos, da microbiota das vias aéreas e dos mediadores inflamatórios na predição das doenças respiratórias, para comparar os efeitos da reabilitação respiratória realizada nos hospitais e na comunidade e para identificar os doentes que mais podem beneficiar de reabilitação respiratória. Os resultados poderão ser utilizados para publicação em revistas científicas e usados em projetos finais de curso, dissertações de mestrado ou teses de doutoramento, sem que haja qualquer quebra de confidencialidade/anonimato.

Condições e financiamento: A participação no estudo é totalmente voluntária. Se decidir participar ser-lhe-á pedido que assine este formulário de consentimento informado (a consentir que recebeu informação sobre o estudo, clarificou as suas dúvidas e aceita participar voluntariamente) mas, é totalmente livre de desistir a qualquer momento, sem que para tal tenha de dar qualquer justificação. A decisão de desistir ou de não participar, não afetará a qualidade dos serviços de saúde ou qualquer outro, que lhe são prestados agora ou no futuro, não o prejudicando de qualquer forma. Não se antecipam inconvenientes da participação no estudo. A probabilidade de se observarem eventos adversos durante a intervenção ou avaliação é muito baixa (e.g., dessaturação de oxigénio, dor no peito). Mesmo assim, para prevenir quaisquer riscos, os participantes terão a frequência cardíaca e saturação periférica de oxigénio monitorizadas continuamente, e em qualquer ocorrência adversa, os testes serão interrompidos e repouso ou qualquer outro cuidado necessário será prestado.

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[1] http://portal.arsnorte.min-saude.pt/portal/page/portal/ARSNorte/Comiss%C3%A3o%20de%20%C3%89tica/Ficheiros/Declaracao_Helsinquia_2008.pdf

[2] http://dre.pt/pdf1sdip/2001/01/002A00/00140036.pdf

[3] https://protecao-dados.pt/wp-content/uploads/2017/07/Regulamento-Geral-Prote%C3%A7%C3%A3o-Dados.pdf

As recolhas de dados serão realizadas nos hospitais, centros de saúde ou na comunidade. Nos hospitais e centros de saúde, sempre que possível, as recolhas serão realizadas durante os períodos de consultas/sessões de tratamento para não causar nenhum transtorno adicional ou deslocações extra. As avaliações e os programas de reabilitação respiratória serão gratuitos, no entanto, os participantes terão de assegurar os custos de deslocações. Não estão contempladas quaisquer compensações monetárias pela participação no estudo, no entanto os participantes poderão receber uma intervenção, considerada fundamental por todas as referências internacionais, para gestão das doenças respiratórias de forma gratuita. Caso seja solicitado, serão também fornecidos os resultados ao participante, para que seja do seu conhecimento e para que os possa mostrar à equipa de saúde que habitualmente o acompanha. Para além disso, a informação obtida neste estudo, através da sua participação, poderá vir a ajudar a melhorar o acesso dos milhares de doentes que sofrem de doença respiratória a uma intervenção qualificada.

Confidencialidade e anonimato: Todos os dados no projeto serão recolhidos ao abrigo do Regulamento Geral de Proteção de Dados (RGPD), em vigor desde 25 de maio de 2018 com respeito à política de privacidade da Universidade de Aveiro (https://www.ua.pt/privacidade). Assim, a informação recolhida durante o estudo será confidencial e anónima. A cada doente será atribuído um código que será utilizado em todas as bases de dados. A folha de registo com os dados pessoais estará guardada num local seguro e de acesso controlado nas instalações da Universidade de Aveiro, onde apenas os investigadores responsáveis pelo trabalho têm acesso. As informações pessoais serão destruídas assim que as análises no âmbito deste projeto terminarem. As bases de dados estarão codificadas/anonimizadas e guardadas num sistema centralizado da Universidade de Aveiro de acesso exclusivo aos investigadores. Em nenhum caso, será tornada pública qualquer informação de identificação dos participantes.

Muito obrigada pela sua leitura! Para quaisquer esclarecimentos adicionais, por favor contacte a bolseira de investigação – Ana Alves, telemóvel – 913858695, e-mail: anaqalves@ua.pt ou a investigadora responsável – Alda Marques, Professora Adjunta da Escola Superior de Saúde da Universidade de Aveiro e Investigadora do Instituto de Biomedicina da Universidade de Aveiro (iBiMED), telefone – 234 372 462, e-mail: amarques@ua.pt

Assinatura do investigador que recolhe o consentimento informado:

… … … … … … … … ….... … … … ….... … … … Data: …… /…… /……..

Declaro ter lido e compreendido este documento, bem como as informações verbais que me foram fornecidas pela/s pessoa/s que acima assina/m. Foi-me garantida a possibilidade de, em qualquer altura, recusar participar neste estudo sem qualquer tipo de consequências, sendo para isso bastante um telefonema, um email, ou qualquer outra forma simples de comunicação com a Investigadora responsável, Drª Alda Marques. Desta forma, aceito participar neste estudo e permito a utilização dos dados para as finalidades aqui descritas, que de forma voluntária forneço, confiando em que apenas serão utilizados para esta investigação e nas garantias de confidencialidade e anonimato que me são dadas pelo/a investigador/a.

Nome: … … … … … … … ….... … … … ….... … … … … … … … … … … … …

Assinatura: … … … … … … … ….... … … … … … .. … … … … … … … … … … … …

Data: …… /…… /……..

SE NÃO FOR O PRÓPRIO A ASSINAR POR IDADE OU INCAPACIDADE

(se o menor tiver discernimento deve também assinar em cima, se consentir)

NOME: …

BI/CC Nº: ..... DATA OU VALIDADE ….. /…. /……..

GRAU DE PARENTESCO OU TIPO DE REPRESENTAÇÃO: .....

ASSINATURA …

ESTE DOCUMENTO É COMPOSTO DE 2 PÁGINA/S E FEITO EM DUPLICADO:

UMA VIA PARA O/A INVESTIGADOR/A, OUTRA PARA A PESSOA QUE CONSENTE