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Dissertação submetida à Escola Superior de Saúde para cumprimento dos requisitos necessários à obtenção do grau de Mestre em Fisioterapia – Opção Cardiorrespiratória, realizada sob a orientação científica da Professora Doutora Alda Marques, Professora Ajunta da Escola Superior de Saúde da Universidade de Aveiro, e coorientação do Mestre Pedro Matos da Silva, Assistente Convidado da Área Técnico-científica da Fisioterapia.

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Effects of a community-based pulmonary rehabilitation programme during acute exacerbations of chronic obstructive pulmonary disease

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Resumo

Introdução: A reabilitação respiratória (RR) é uma intervenção essencial na gestão da doença pulmonar obstrutiva crónica (DPOC) estável, com o potencial de ser igualmente eficaz nas exacerbações agudas (EADPOC). Contudo, o seu papel durante as EADPOC é ainda controverso pois a maioria dos estudos têm sido conduzidos em pacientes severos e hospitalizados, quando mais de 80% das EADPOC são geridas na comunidade. **Objetivo:** Este estudo avaliou os efeitos de um programa de RR comunitário durante as EADPOC. **Métodos:** 23 pacientes com EADPOC foram alocados voluntariamente ao grupo experimental (GE: n=12, 69±7anos, FEV_1 52±27pp) ou controlo (GC: n=11, 66±9anos, FEV_1 55±22pp). O GC recebeu tratamento farmacológico. O GE recebeu tratamento farmacológico e 3 semanas (2 sessões/semana) de RR (i.e., controlo ventilatório e técnicas de higiene brônquica, exercícios de mobilidade e expansibilidade torácica, exercício físico e apoio psicoeducativo). A frequência cardíaca, frequência respiratória (FR), saturação periférica de oxigénio (SpO_2), escala modificada Medical Research Council (mMRC), dispneia e fadiga em repouso com a escala modificada de Borg, força muscular do quadricípite (FMQ), o teste 5-repetições sentar-levantar e o questionário de avaliação da DPOC (CAT) foram avaliados até 48h do diagnóstico de EADPOC (Pré) e após a RR (Pós). Calcularam-se as diferenças entre Pré/Pós e os tamanhos do efeito (ES). **Resultados:** Após a RR, apenas o GE apresentou melhorias significativas na FR, SpO_2, dispneia em repouso, FMQ e CAT. Na comparação entre grupos, o GE melhorou de forma significativamente superior ao GC na FR (p=0.015; ES=-0.92), FMQ (p=0.034; ES=0.88) e CAT (p=0.013; ES=-1.10). Não foram reportados efeitos adversos. **Conclusão:** A RR na comunidade parece ser uma intervenção segura e eficaz para a gestão das EADPOC, tendo demonstrado benefícios semelhantes aos já bem estabelecidos para a RR na DPOC estável. Estudos randomizados e com amostras maiores são necessários para verificar estes resultados.

Palavras-chave: Exacerbações agudas da DPOC; Reabilitação respiratória; Comunidade

Abstract

Background: Pulmonary rehabilitation (PR) is a cornerstone intervention for the management of stable chronic obstructive pulmonary disease (COPD) with the potential of being equally effective in acute exacerbations (AECOPD). However, its role during AECOPD is still controversial since most studies have been conducted in hospitalised and severe patients, when more than 80% of AECOPD are in fact managed on an outpatient basis. **Aim:** This study aimed to assess the effects of a community-based PR programme during AECOPD. **Methods:** 23 patients with AECOPD were voluntarily allocated to the experimental (EG: n=12, 69±7years, FEV_1 52±27pp) or control group (CG: n=11, 66±9years, FEV_1 55±22pp). The CG received standard medication. The EG received standard medication plus 3 weeks (2 sessions/week) of PR (i.e., breathing control and airway clearance techniques, thoracic mobility and expansion exercises, exercise training and psychoeducational support). Heart rate, respiratory rate (RR), peripheral oxygen saturation (SpO_2), modified Medical Research Council dyspnoea questionnaire (mMRC), dyspnoea and fatigue at rest with the modified Borg scale, quadriceps muscle strength (QMS), the 5-repetition sit-to-stand test and the COPD Assessment test (CAT) were assessed within 48h of the AECOPD onset (Pre) and after PR (Post). Differences between Pre/Post PR and effect sizes (ES) were calculated. **Results:** After PR, significant improvements were observed in the EG on RR, SpO_2, dyspnoea at rest, QMS and CAT. No significant differences were found in the CG. In the between groups comparison, the EG presented improvements significantly superior than those in the CG on RR (p=0.015; ES=-0.92), QMS (p=0.034; ES=0.88) and CAT (p=0.013; ES=-1.10). No adverse events were reported. **Conclusion:** Community-based PR seems to be a safe and effective intervention during AECOPD managed on an outpatient basis. It provided similar benefits to those well-established for PR in stable COPD. Randomised studies with larger samples are needed to verify these results.

Key words: Acute exacerbations of COPD; Pulmonary rehabilitation; Community

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive and life-threatening condition characterised by persistent respiratory symptoms and airflow limitation (The Global Initiative for Chronic Obstructive Lung Disease, 2018). It affects 384 million people in the world and 800.000 in Portugal (De Araújo, 2016; The Global Initiative for Chronic Obstructive Lung Disease, 2018). Currently, COPD is a leading cause of morbidity and mortality worldwide, being responsible for about 6% of all deaths in 2012 (The Global Initiative for Chronic Obstructive Lung Disease, 2018). Consequently, COPD imposes a substantial and increasing health, economic and social burden (The Global Initiative for Chronic Obstructive Lung Disease, 2018).

The trajectory of COPD is frequently punctuated by exacerbations, defined as episodes of acute worsening of respiratory symptoms that result in additional therapy (The Global Initiative for Chronic Obstructive Lung Disease, 2018; Wedzicha et al., 2017). Acute exacerbations of COPD (AECOPD) account for more than 70% of all COPD-related costs (Puhan, Gimeno-Santos, Cates, & Troosters, 2016) and are the main responsible for patients' clinical deterioration (The Global Initiative for Chronic Obstructive Lung Disease, 2018). These events have a negative impact on patients' health status and disease progression, resulting in declines on lung function, physical activity levels, muscle strength, functional capacity and health-related quality of life, and increasing patients' susceptibility to more exacerbations, hospitalisations and death (Cote, Dordelly, & Celli, 2007; S. E. Jones et al., 2018; The Global Initiative for Chronic Obstructive Lung Disease, 2018; Wedzicha et al., 2017). In fact, it is known that the five-year mortality rate after a hospitalisation for AECOPD is around 50% (The Global Initiative for Chronic Obstructive Lung Disease, 2018). Treatment goals for patients with AECOPD are, therefore, to minimise the negative impact of these events and prevent their recurrence (The Global Initiative for Chronic Obstructive Lung Disease, 2018).

Pulmonary rehabilitation (PR) is a comprehensive intervention based on a thorough patient assessment followed by tailored therapies such as, exercise training, education, and behaviour change, designed to improve the physical and psychological condition of patients with chronic respiratory diseases (Spruit et al., 2013). Currently, PR is the most well-established and one of the most cost-effective interventions for the management of patients with stable COPD (evidence grade A) (Rochester et al., 2015; The Global Initiative for Chronic Obstructive Lung Disease, 2018). It has been shown to: i) improve exercise capacity, functional capacity, muscle strength and health-related quality of life; ii) reduce symptoms, hospitalisations and unscheduled healthcare visits; and iii) enhance self-management and self-efficacy (Rochester et al., 2015). Given these benefits it would seem reasonable to consider PR as a management

strategy for AECOPD as well (Spruit et al., 2013). However, studies assessing the role of PR during AECOPD have shown controversial results (Puhan et al., 2016; Spruit et al., 2018; The Global Initiative for Chronic Obstructive Lung Disease, 2018; Wedzicha et al., 2017).

This controversy among studies is probably related to the settings in which the PR programmes have been conducted and the severity of the patients included. Most studies have been conducted in hospitalised patients with AECOPD (Machado, Silva, Afreixo, & Marques, 2018; Oliveira & Marques, 2017; Puhan et al., 2016), who present more severe exacerbations and/or more severe underlying disease than those managed on an outpatient setting (The Global Initiative for Chronic Obstructive Lung Disease, 2018). Nevertheless, those are in fact a small portion of patients with AECOPD, as more than 80% of all AECOPD are managed on an outpatient basis (The Global Initiative for Chronic Obstructive Lung Disease, 2018). Therefore, studies conducting PR programmes in patients with AECOPD managed on an outpatient basis are needed to establish the role of PR during AECOPD (Machado et al., 2018).

This study aimed to assess the effects of a community-based PR programme during AECOPD.

2. Methods

This study is part of a larger study entitled "GENIAL – Genetic and clinical markers in COPD trajectory", funded by Programa Internacional de Competitividade e Internacionalização – POCI, through Fundo Europeu de Desenvolvimento Regional – FEDER (POCI-01-0145-FEDER-007628), Fundação para a Ciência e Tecnologia (PTDC/DTP-PIC/2284/2014) and under the project UID/BIM/04501/2013. Several publications have been developed in the scope of this dissertation (Appendix 1).

2.1. Study design

A quasi-experimental study was conducted.

2.2. Sample

Non-hospitalised patients with AECOPD were recruited via clinicians at Centro Hospitalar do Baixo Vouga (Aveiro), Hospital Pedro Hispano (Matosinhos) and Hospital Distrital da Figueira da Foz between November 2016 and December 2017. Inclusion criteria were diagnosis of AECOPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria (The Global Initiative for Chronic Obstructive Lung Disease, 2018). Exclusion criteria were: i) hospitalisation; ii) presence of severe co-existing respiratory, neurological (e.g., Parkinson's disease), cardiac (e.g., uncontrolled symptomatic heart failure), musculoskeletal

(e.g., kyphoscoliosis), or psychiatric impairments; iii) current neoplasia or immunological disease; and iv) any therapeutic intervention in addition to standard of care.

According to the recommendations for adequate sample sizes to conduct pilot studies, 12 participants in each group would be needed to conduct this study (Julious, 2005). However, as it is known that dropout rates in respiratory interventions are around 30-35% (Garrod, Marshall, Barley, & Jones, 2006), 16 patients in each group were aimed to be recruited.

2.3. Measures

A structured questionnaire was first used to collect sociodemographic (age, gender), anthropometric (height, weight, body mass index – BMI) and general clinic (smoking habits, number of exacerbations in the past year, medication used in the stable and exacerbated period of the disease, long-term oxygen, non-invasive ventilation, comorbidities and physical activity levels) data. Physical activity level was assessed with the brief physical activity assessment tool, which is a simple, quick and reliable instrument that is being validated for use in COPD and has been significantly correlated with the international physical activity questionnaire ($r=0.523$, $p<0.001$), accelerometers ($r=0.529$, $p<0.001$) and daily steps ($r=0.565$, $p<0.001$) (Cruz, Jácome, & Marques, 2017; Marshall, Smith, Bauman, & Kaur, 2005). It comprises two questions regarding the frequency and duration of moderate and vigorous physical activity undertaken in an usual week (Marshall et al., 2005). Each question is scored from 0 to 4 and the total score consists of summing the result of the two questions, ranging from 0 to 8 (Marshall et al., 2005). Scores of 0-3 are considered "insufficiently active", and scores higher or equal to 4 "sufficiently active" (Marshall et al., 2005).

In each data collection moment, dyspnoea during activities, vital signs (i.e., respiratory and heart rates), peripheral oxygen saturation (SpO_2), symptoms of dyspnoea and fatigue at rest, quadriceps muscle strength, functionality and impact of the disease were collected by a trained physiotherapist following the described standardised order.

Dyspnoea during activities was assessed with the modified British Medical Research Council dyspnoea questionnaire (mMRC), which comprises five grades in a scale from 0 to 4, with higher grades indicating greater perceived dyspnoea (Crisafulli & Clini, 2010). This is a simple, valid and widely used instrument to characterise the impact of dyspnoea on the daily activities of patients with COPD, that has been well-related with other measures of health status and predicts mortality risk (The Global Initiative for Chronic Obstructive Lung Disease, 2018). Patients with scores superior or equal to 2 have been classified as "more breathlessness" and those with scores inferior to 2 as "less breathlessness" (The Global Initiative for Chronic Obstructive Lung Disease, 2018). Variations of 1 unit have been established as the minimal clinically important difference (MCID) for stable patients with COPD after PR (De Torres et

al., 2002). Regarding to AECOPD, a MCID of 0.5 units after pharmacological treatment has recently been indicated (Oliveira, Andrade, & Marques, 2017).

Vital signs, SpO_2 and symptoms of dyspnoea and fatigue at rest were assessed whilst participants were sitting and resting for at least 10 minutes. Respiratory rate was assessed during 60 seconds by direct observation of the chest wall (Wallis, Healy, Undy, & Maconochie, 2005). Heart rate and SpO_2 were collected with a pulse oximeter (Pulsox 300i, Konica Minolta, Singapore, China). In AECOPD, SpO_2 has been shown to have high sensitivity and specificity to detect both hypoxemia (sensitivity=83.9%, specificity=88.9%) and hypercapnia (sensitivity=71.3%, specificity=76%), and has been positively correlated with arterial oxygen saturation ($r=0.91$; $p<0.001$) (Oliveira & Marques, 2017). Dyspnoea and fatigue were assessed by asking participants to rate their perceived levels of these symptoms on the modified Borg scale (mBorg), a vertical scale that ranges from 0 to 10 and has verbal expressions anchored to the numbers (Borg, 1982; Kendrick, Baxi, & Smith, 2000). Higher grades indicate greater perceived intensity of the symptom (Borg, 1982; Kendrick et al., 2000). The MCID established for dyspnoea symptoms in the mBorg is of 1 unit for stable patients with AECOPD after PR (Ries, 2005) and 1 unit for patients with AECOPD receiving pharmacological treatment (Oliveira et al., 2017).

Quadriceps muscle strength was measured as peak torque during an isometric contraction of the quadriceps of the dominant side with a handheld dynamometer (microFET2, Hoggan Health, The best Salt Lake City, Utah), which has shown good test-retest reliability (ICC=0.87) (O'Shea, Taylor, & Paratz, 2007). Patients were sited with the knee and hip flexed at 90º and were instructed to perform a maximal contraction (Bohannon, 1986). The assessor kept the dynamometer stable proximal to the ankle, on the anterior surface of the leg, and gave verbal encouragement during the test (Bohannon, 1986). The best of 3 manoeuvres was considered for the analysis. Reference values for clinical interpretation of results are available for healthy adults and older people (Andrews, Thomas, & Bohannon, 1996; Bohannon, 1997).

Functionality was assessed with the five-repetition sit-to-stand test (5-STS), which is a valid, reliable (ICC=0.97) and responsive measure in patients with stable COPD that has been significantly correlated to exercise capacity ($r=-0.59$, $p<0.001$) (S. E. Jones et al., 2013). A straight-backed armless chair of 48cm, with a hard seat, stabilised against a wall was used to perform the test (S. E. Jones et al., 2013). Seated participants were asked to cross their arms at the chest and then to stand up all the way and sit down, as fast as possible, for five times without using the arms (S. E. Jones et al., 2013). The protocol of Jones et al. 2013 was followed (S. E. Jones et al., 2013). The best time of 3 trials was considered for the analysis. A cut-off of 12 seconds has been defined to determinate patients at risk of falling (Tiedemann, Shimada,

Sherrington, Murray, & Lord, 2008). A MCID of 1.7 seconds has been established for patients with stable COPD after PR (S. E. Jones et al., 2013). There is no MCID established for AECOPD.

Impact of the disease was measured with the COPD Assessment Test (CAT). CAT is a disease-specific questionnaire consisting of eight items (i.e., cough, sputum, chest tightness, breathlessness going up hills/stairs, activity limitations at home, confidence leaving home, sleep and energy) scored from 0 to 5 (P. Jones et al., 2009). The individual score of each item is added to provide a total score that can range from 0 to 40 (P. Jones et al., 2009). Total scores inferior to 10 are considered as "reduced impact", from 10-20 as "medium impact", from 21-30 as "high impact" and above 30 as "very high impact" (P. W. Jones, Tabberer, & Chen, 2011). CAT is a valid and reliable instrument for use in patients with AECOPD (Chronbach's alpha=0.88) and has been highly correlated with other measures of health status (Oliveira & Marques, 2017). A MCID of 2 points for patients with AECOPD receiving pharmacological treatment has been established (Kon et al., 2014).

All patients were classified accordingly to the GOLD spirometric grades and stages (The Global Initiative for Chronic Obstructive Lung Disease, 2018). Severity of airflow limitation was classified based on the stable spirometry from the clinical notes (The Global Initiative for Chronic Obstructive Lung Disease, 2018). The ABCD assessment tool was used to determinate GOLD stages based on the number of exacerbations in the previous year and mMRC collected at the baseline assessment (The Global Initiative for Chronic Obstructive Lung Disease, 2018).

2.4. Procedures

Eligible patients were identified by clinicians and contacted by the researchers, who explained the purpose of the study and asked about their willingness to participate. An appointment with the researchers was then scheduled within 48 hours of the diagnosis of AECOPD with those interested to participate. At those appointments, researchers clarified any remaining doubts about the study, collected the signed informed consents and performed the baseline assessments (Pre).

Participants were then assigned, accordingly to their preference and convenience, to the experimental (EG) or the control (CG) groups. After 3 weeks, all participants were assessed again (Post) independently of group allocation.

2.4.1. *Intervention*

The intervention consisted on standard medical treatment for the CG (i.e., medication and rest) and standard medical treatment plus a community-based PR programme for the EG.

The community-based PR programme was performed twice a week for 3 weeks (6 sessions). This total duration for the intervention was chosen because it is known that the period of time needed to recover from a lower respiratory tract infection is 21 days or less, and these infections account for 70-80% of all AECOPD (Qureshi, Sharafkhaneh, & Hanania, 2014; Woodhead et al., 2011).

The mean duration of each session was 60 minutes and included breathing control and airway clearance techniques, thoracic expansion and mobility exercises, exercise training and psychoeducational support (Machado et al., 2018; Marques, Oliveira, & Oliveira, 2016; Oliveira & Marques, 2016; Puhan et al., 2016).

Airway clearance techniques (i.e., slow inspiratory/expiratory techniques and active cycle of breathing techniques) were performed following the pulmonary auscultation and based on its findings (Postiaux, 2014). Exercise training was prescribed via Karvonen formula (Karvonen & Vuorimaa, 1988) at an intensity of 60-80% of patients' maximum estimated heart rate (Fox 3rd, Naughton, & Haskell, 1971; Goldberg, Elliot, & Kuehl, 1988). All patients were monitored during the sessions based on their heart rate, SpO_2 and symptoms of dyspnoea and fatigue with the mBorg (Jenkins, Hill, & Cecins, 2010; Spruit et al., 2013), where scores of 4-6 were aimed (Spruit et al., 2013).

Sessions were held in a well-equipped room at the Respiratory Research and Rehabilitation Laboratory (Lab3R) of the School of Health Sciences at the University of Aveiro (ESSUA) or at patients' home by a physiotherapist with experience in respiratory interventions. A detailed description of the intervention protocol can be found in Table 1.

Table 1 – Intervention protocol for the 3-week community-based pulmonary rehabilitation programme.

First week			
Techniques/components	**First session**		**Second session**
Psychoeducational support	Education on relaxation and dyspnoea relief positions (10 min)		Clarification of doubts of the 1st session
Breathing retraining	Breathing control (10-15 cycles) Pursed-lips breathing (apnoea for 3-5s, 8 cycles)		Breathing control (10-15 cycles) Deep breathing exercises (5-10 cycles) Pursed-lips breathing (apnoea for 3-5s, 6 cycles)
Slow inspiratory and expiratory techniques*	EDIC and ELTGOL (apnoea for 3-5s, 10 repetitions)		EDIC and ELTGOL (apnoea for 5s, 8 repetitions)
Active cycle of breathing techniques*	Teaching of part of this technique (huffing and cough)		Original cycles (3-5 repetitions)
Warm up (5 min)	Circumduction of upper limbs Flexion and extension of the trunk		Circumduction of upper limbs Lateral flexion of the trunk
Thoracic mobility and expansion exercises (2x10 each exercise)	Proprioceptive neuromuscular facilitation diagonal Rotation of the trunk		Proprioceptive neuromuscular facilitation diagonal (progression 1) Rotation of the trunk (progression 1)
Flexibility/stretch exercises (2-3x30s each exercise)	Lateral flexors of the neck Abductors of upper limbs Adductors of upper limbs		Lateral flexors of the neck (progression 1) Abductors of upper limbs (progression 1) Adductors of upper limbs (progression 1)
Psychoeducational support (flyers)	Breathing control Dyspnoea relief Airway clearance techniques		Respiratory system Lower respiratory tract infections

Second week			
Techniques/components	**Third session**		**Fourth session**
Psychoeducational support	Clarification of doubts of the 2nd session		Clarification of doubts of the 3rd session
Breathing retraining	Breathing control (10-15 cycles) Deep breathing exercises (5 cycles) Pursed-lips breathing plus Acapella (apnoea for 5s, 5 cycles)		Breathing control (10-15 cycles) Deep breathing exercises (5 cycles) Pursed-lips breathing plus Acapella (apnoea for 5s, 5 cycles)
Slow inspiratory and expiratory techniques*	EDIC and ELTGOL plus Acapella (apnoea for 5s, 8 repetitions)		EDIC and ELTGOL plus Acapella (apnoea for 5s, 6 repetitions)
Active cycle of breathing techniques*	Original cycles (3-5 repetitions)		Original cycles (3-5 repetitions)
Warm up (5 min)	Circumduction of upper limbs (progression 1) Lateral flexion of the trunk (progression 1)		Circumduction of upper limbs (progression 1) Lateral flexion of the trunk (progression 2) Step in place
Thoracic mobility and expansion exercises and muscle strength (2x10 each exercise)	Flexion and extension of upper limbs (strengthening) Rotation of the trunk (progression 2)		Proprioceptive neuromuscular facilitation diagonal (progression 2) Squats
Aerobic training			Cycling or Step (interval) or Walking (5 min)
Flexibility/stretch exercises (2-3x30s each exercise)	Elbow extensors Lateral flexors of the trunk Upper limb flexors		Knee extensors Posterior chain muscles Abductors and Adductors of upper limbs
Psychoeducational support (flyers)	Exercise		Nutrition

Third week			
Techniques/components	**Fifth session**		**Sixth session**
Psychoeducational support	Clarification of doubts of the 4th session		Clarification of doubts of the 5th session
Breathing retraining	Deep breathing exercises (5 cycles) Pursed-lips breathing plus Acapella (apnoea for 5s, 5 cycles)		Deep breathing exercises (5 cycles) Pursed-lips breathing plus Acapella (apnoea for 5s, 5 cycles)
Slow inspiratory and expiratory techniques*	EDIC and ELTGOL plus Acapella (apnoea for 5s, 5 repetitions)		EDIC and ELTGOL plus Acapella (apnoea for 5s, 5 repetitions)
Active cycle of breathing techniques*	Original cycles (3-5 repetitions)		Original cycles (3-5 repetitions)
Warm up (5 min)	Circumduction of upper limbs (progression 1) Lateral flexion of the trunk (progression 2) Step in place		Circumduction of upper limbs (progression 1) Lateral flexion of the trunk (progression 2) Step in place
Thoracic mobility and expansion exercises and muscle strength (2x10 each exercise)	Crunches Proprioceptive neuromuscular facilitation diagonal (progression 3) Squats		Crunches Proprioceptive neuromuscular facilitation diagonal (progression 3) Lunges
Aerobic training	Cycling or Step (interval) or Walking (10 min)		Cycling or Step (interval) or Walking (20 min)
Flexibility/stretch exercises (2-3x30s each exercise)	Upper limb abductors and adductors Knee extensors Posterior chain muscles		Upper limb abductors and adductors Knee extensors Posterior chain muscles "Morning stretch"
Psychoeducational support (flyers)	Smoking cessation (if applicable)		

Adapted from Marques, Alda, Oliveira, Ana, & Oliveira, Daniela. (2016). *Gerir a infeção respiratória do trato inferior na comunidade: o papel do Fisioterapeuta*. Lisbon: Lusodidata

*Only applied if needed and based on pulmonary auscultation findings.

Legend: EDIC, exercise with inspiratory controlled flow; ELTGOL, total slow expiration with glottis open in lateral posture.

2.5. Ethics

Approval for this study was first obtained from the ethics committees of the Administração Regional de Saúde do Centro, I.P. (3NOV'2016:64/2016), Centro Hospitalar do Baixo Vouga (22MAR'2017:777638), Hospital Pedro Hispano (17FEB'2017:10/CE/JAS) and Hospital Distrital da Figueira da Foz (18JUL'2017) and from the National Data Protection Committee (8828/2016). Written inform consents were obtained from all participants before any data collection.

2.6. Data analysis

All statistical analyses were performed using IBM SPSS Statistics version 24.0 (IBM Corporation, Armonk, NY, USA). The level of significance was set at 0.05.

Descriptive statistics were used to describe the sample. First, the normality of the data was explored with the Shapiro-Wilk test. Then, independent t tests for continuous data with normal distribution, Mann-Whitney U tests for ordinal data and continuous data without normal distribution, and chi-squared tests for categorical data were used to compare sociodemographic, anthropometric and general clinical characteristics.

As not all the assumptions for carrying out a mixed-methods ANOVA were fulfilled, the differences between pre- and post-intervention assessments, per group, were pooled for each outcome measure and Mann-Whitney U tests were used to compare the groups. Comparisons between pre- and post-intervention assessments within each group were performed with Wilcoxon signed-rank tests.

Effect sizes (ES) were calculated as Cohen's d via the mean pre-post change in each group, according to the pretest-posttest-control design formula (Morris, 2008), and interpreted as small (≥0.2), medium (≥0.5) or large (≥0.8) (Cohen, 1988). Whenever possible, the number and percentage of participants in each group that improved above the MCID was determined.

3. Results

Thirty-five non-hospitalised patients with AECOPD were referred for possible inclusion in the study. From these, three were excluded due to presenting sequels of cerebrovascular accident that impaired her/his ability to perform the assessments (n=1), suffered from Parkinson's disease (n=1) or had a diagnosis of interstitial lung disease (n=1). Thus, 32 patients were invited to participate in the study and allocated to either the experimental or control group accordingly to their preference and convenience. Three patients in the EG and 6 in the CG dropped out of the study. Therefore, 23 patients (12 in the EG and 11 in the CG) were included (Figure 1).

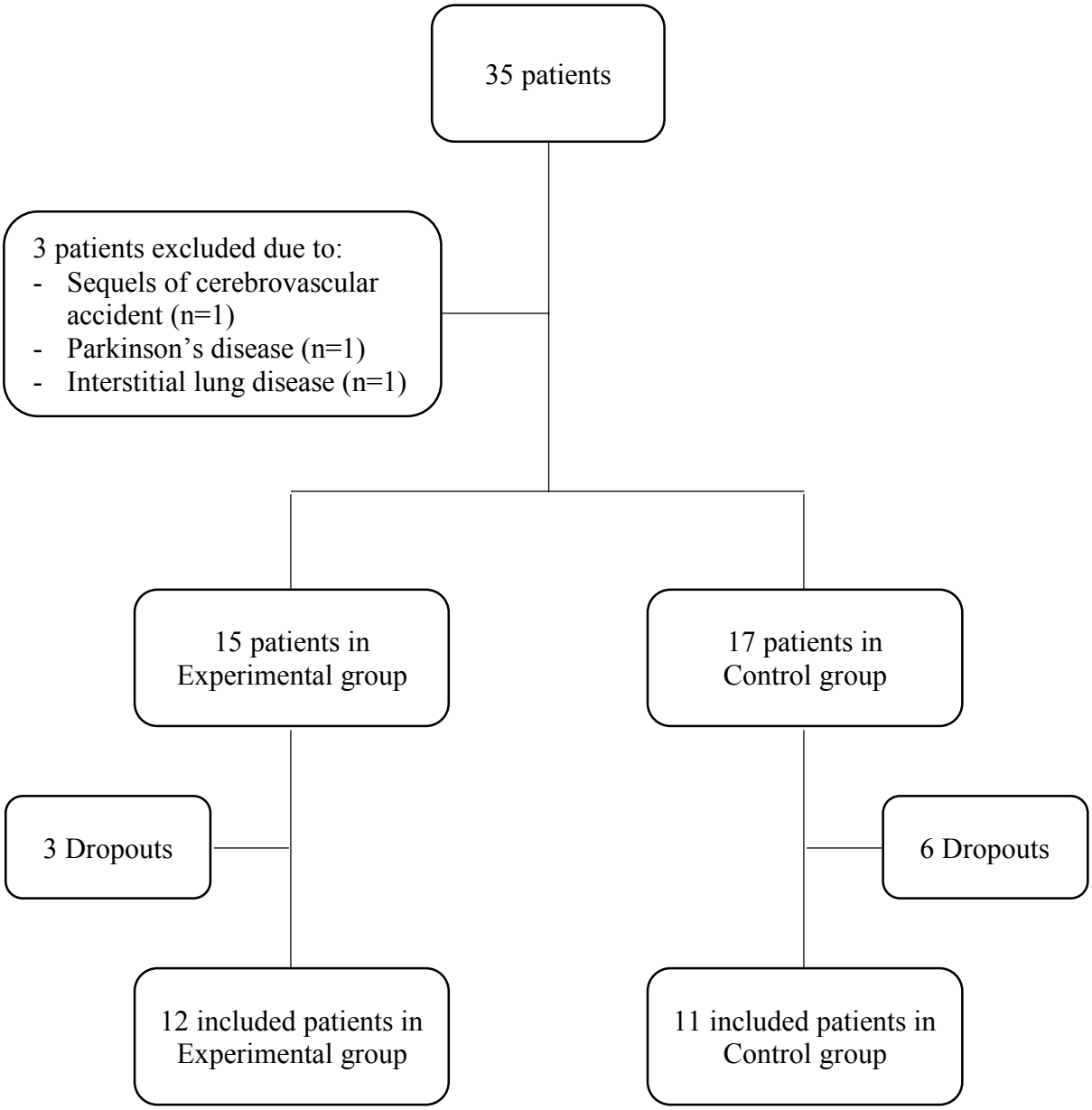

Figure 1 – Flow diagram of participants through the study.

There were no significant differences between completers and dropouts in terms of age and gender ($p>0.05$).

Included patients were mainly male (n=19, 82.6%) and former smokers (n=15, 65.2%), with a mean age of 67.3±8.0 years old, a mean forced expiratory volume in one second of 57.2±23.9% of predicted and a mean BMI of 27.2±4.3kg/m^2. Regarding to airflow limitation, most patients were in GOLD grades II (n=7, 30.4%) or III (n=7, 30.4%), i.e., moderate to severe obstruction. GOLD stage D, i.e., symptomatic patients with frequent exacerbations, was the most prevalent (n=11, 47.8%). Diabetes (n=9, 39.1%) and hypertension (n=9, 39.1%) were the comorbidities most observed. Patients presented low levels of physical activity (median 0.0, interquartile range [0.0; 4.0]). Baseline characteristics of the sample per group are shown in Table 2. No significant differences were observed between groups ($p>0.05$).

Table 2 – Sample characterisation (n=23).

Characteristics	Experimental group (n=12)	Control group (n=11)	Test value	p-value
Age, years	68.6±7.4	65.8±8.8	t=-0.820	0.421
Gender, n (%)			χ^2=0.009	1.000
Male	10 (83.3)	9 (81.8)		
Female	2 (16.7)	2 (18.2)		
BMI, kg/m^2	26.8±3.2	27.6±5.5	t=0.410	0.686
Smoking status, n (%)			χ^2=1.559	0.600
Current	1 (8.3)	3 (27.3)		
Former	9 (75.0)	6 (54.5)		
Never	2 (16.7)	2 (18.2)		
Packs/year	26.5 [2.7; 57.5]	27.0 [7.4; 60.0]	U=60.500	0.751
Exacerbations/year	2.0 [1.0; 1.8]	1.0 [0.0; 2.0]	U=47.500	0.253
FEV_1, L	1.3±0.7	1.4±0.5	t=0.344	0.734
FEV_1, %predicted	51.5±26.6	55.0±21.5	t=0.344	0.735
FVC, L	2.7±0.7	2.6±0.7	t=-0.212	0.834
FVC, %predicted	81.6±24.6	78.5±18.5	t=-0.346	0.733
FEV_1/FVC, %	48.3±16.8	53.1±12.0	t=0.787	0.440
GOLD stages, n (%)			χ^2=0.443	1.000
I	3 (25.0)	2 (18.2)		
II	3 (25.0)	4 (36.4)		
III	4 (33.3)	3 (27.3)		
IV	2 (16.7)	2 (18.2)		
GOLD groups, n (%)			χ^2=1.778	0.676
A	1 (8.3)	3 (27.3)		
B	3 (25.0)	3 (27.3)		
C	1 (8.3)	1 (9.1)		
D	7 (58.3)	4 (36.4)		
Physical activity	0.0 [0.0; 7.3]	0.0 [0.0; 0.0]	U=42.500	0.070
Non-invasive ventilation, n (%)	3 (25.0)	2 (18.2)	χ^2=0.157	1.000
Long-term oxygen therapy	3 (25.0)	2 (18.2)	χ^2=0.157	1.000

Comorbidities					χ^2=0.491	0.590
Benign prostatic hyperplasia		3 (25.0)		1 (9.1)		
Diabetes		2 (16.7)		2 (18.2)		
Dyslipidaemia		6 (50.0)		3 (27.3)		
Heart condition		4 (33.3)		1 (9.1)		
Hypertension		5 (41.7)		4 (36.4)		
History of cerebrovascular accident		1 (8.3)		1 (9.1)		
History of neoplasia		1 (8.3)		2 (18.2)		
Obstructive sleep apnoea		1 (8.3)		2 (18.2)		
Peripheral vascular condition		2 (16.7)		0 (0.0)		
Others		3 (25.0)		2 (18.2)		
Medication use, n (%)	Stability	AECOPD (extra)	Stability	AECOPD (extra)	χ^2=2.640	0.195
Antibiotics	1 (8.3)	5 (41.7)	1 (9.1)	9 (81.8)		
Antihistaminic	0 (0.0)	2 (16.7)	0 (0.0)	0 (0.0)		
Antipyretics	0 (0.0)	1 (8.3)	3 (27.3)	2 (18.2)		
Antitussive	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)		
Bronchodilators						
Beta-adrenergic agonists	4 (33.3)	0 (0.0)	3 (27.3)	0 (0.0)		
Cholinergic antagonists	9 (75.0)	0 (0.0)	3 (27.3)	1 (9.1)		
Anti-inflammatory	5 (41.7)	1 (8.3)	2 (18.2)	1 (9.1)		
Xanthines	6 (50.0)	0 (0.0)	1 (9.1)	0 (0.0)		
Associations of bronchodilators with cholinergic antagonists	10 (83.3)	2 (16.7)	5 (45.5)	3 (27.3)		
Corticosteroids	0 (0.0)	2 (16.7)	0 (0.0)	1 (9.1)		
Expectorants	3 (25.0)	5 (41.7)	1 (9.1)	5 (45.5)		

Values are presented as mean±standard deviation or median [interquartile range], unless otherwise stated.

Legend: AECOPD, acute exacerbation of chronic obstructive pulmonary disease; BMI, body mass index; FVC, forced vital capacity; FEV_1, forced expiratory volume in one second; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

In the baseline assessment, patients in both groups presented symptoms of dyspnoea in the mMRC (EG: 2.5 [1.3; 3.0]; CG: 2.0 [1.0; 3.0]) and in the mBorg (EG: 3.0 [0.5; 3.8]; CG: 3.0 [0.0; 4.0]). Regarding to fatigue, the EG (3.0 [0.9; 6.3]) was more symptomatic than the CG (0.0 [0.0; 3.0]). Both groups presented an elevated respiratory rate (EG: 24.0 [205; 27.0]; CG: 20.0 [18.0; 24.0]) and accentuated quadriceps muscle weakness (EG: 21.0 [19.7; 27.2]; CG: 14.8 [8.7; 19.2]). Performance in the 5-STS was below the cut-off for risk of falling in both groups (EG: 9.4 [6.9; 13.0]; CG: 7.6 [5.6; 9.8]). CAT total score was of "high impact" in both groups (EG: 23.0 [19.3; 24.8]; CG: 21.0 [14.0; 28.0]) (Table 3).

After the community-based PR programme, significant improvements were found in the EG on symptoms of dyspnoea at rest (Pre 3.0 [0.5; 3.8] vs. Post 1.0 [0.0; 2.8], p=0.008), respiratory rate (Pre 24.0 [20.5; 27.0] vs. Post 20.5 [18.0; 23.5], p=0.004), SpO_2 (Pre 94.0 [89.3; 96.0] vs. Post 96.0 [94.3; 96.0], p=0.031), quadriceps muscle strength (Pre 21.0 [19.7; 27.2] vs. Post 25.0 [22.4; 28.8], p=0.012) and impact of the disease (Pre 23.0 [19.3; 24.8] vs. Post 14.5 [6.3; 19.5], p=0.008). No differences were found in the remaining outcome measures. The CG did not present any significant differences after the intervention (p>0.05) (Table 3).

In the between groups comparison, the EG showed significant improvements when compared to the CG on respiratory rate (EG -3.5 [-4.0; -0.5] vs. CG 2.0 [0.0; 4.0], p=0.015), quadriceps muscle strength (EG 3.1 [1.9; 7.2] vs. CG 0.3 [-1.5; 1.8], p=0.034) and impact of the disease assessed with the CAT (EG -6.0 [-15.0; -4.0] vs. CG 0.0 [-8.0; 3.0], p=0.013). No additional differences were found (p>0.05) (Table 3).

Large effects were found on respiratory rate (ES=-0.92), quadriceps muscle strength (ES=0.88) and CAT (ES=-1.10). Dyspnoea in the mMRC (ES=-0.63), heart rate (ES=-0.56) and symptoms of fatigue in the mBorg (ES=-0.70) presented moderate effects. Dyspnoea in the mBorg (ES=-0.33), SpO_2 (ES=0.17) and 5-STS (ES=0.00) presented small and negligible effects, respectively. No adverse events were reported.

In the EG, improvements above the MCID were observed in 6 (50.0%) patients on the mMRC, 8 (66.7%) on dyspnoea in the mBorg, 3 (23.0%) on the 5-STS and 11 (91.7%) on CAT. In the CG, improvements above the MCID were only observed in 4 (36.4%) patients on the mMRC, 5 (45.5%) on dyspnoea in the mBorg, 2 (18.2%) on the 5-STS and 5 (45.5%) on CAT (Figure 2).

Table 3 – Descriptive and inferential statistic before and after the acute exacerbation of chronic obstructive pulmonary disease (n=23).

	Experimental group				Control group				Between groups				
	Pre	**Post**	**Test value (Z)**	**p-value**	**Pre**	**Post**	**Test value (Z)**	**p-value**	**Diff EG**	**Diff CG**	**Test value (U)**	**p-value**	**ES**
mMRC grade	2.5 [1.3; 3.0]	1.5 [0.3; 1.8]	-1.933	0.094	2.0 [1.0; 3.0]	2.0 [1.0; 3.0]	0.000	1.000	-0.5 [-1.0; 0.0]	0.0 [-1.0; 1.0]	47.000	0.241	-0.63
Heart rate (bpm)	76.0 [74.0; 95.0]	74.0 [62.3; 86.8]	-1.773	0.076	82.0 [67.0; 91.0]	79.0 [73.0; 91.0]	-0.267	0.831	-1.5 [-17.0; 0.5]	-4.0 [-7.0; 12.0]	52.000	0.404	-0.56
Respiratory rate (cpm)	24.0 [20.5; 27.0]	20.5 [18.0; 23.5]	-2.721	0.004*	20.0 [18.0; 24.0]	20.0 [18.0; 24.0]	-0.704	0.523	-3.5 [-4.0; -0.5]	2.0 [0.0; 4.0]	27.500	0.015*	-0.92
SpO_2 (%)	94.0 [89.3; 96.0]	96.0 [94.3; 96.0]	-2.257	0.031*	93.0 [92.0; 94.0]	95.0 [91.0; 96.0]	-1.798	0.074	1.0 [0.0; 3.8]	1.0 [0.0; 3.0]	64.500	0.940	0.17
Dyspnoea (mBorg)	3.0 [0.5; 3.8]	1.0 [0.0; 2.8]	-2.565	0.008*	3.0 [0.0; 4.0]	0.0 [0.0; 3.0]	-0.997	0.422	-1.0 [-2.0; 0.0]	0.0 [-3.0; 1.0]	52.000	0.393	-0.33
Fatigue (mBorg)	3.0 [0.9; 6.3]	2.0 [0.3; 3.0]	-1.919	0.059	0.0 [0.0; 3.0]	0.0 [0.0; 4.0]	-0.769	0.516	-1.0 [-2.0; 0.0]	0.0 [-2.0; 3.0]	42.000	0.138	-0.70
QMS (kgf)	21.0 [19.7; 27.2]	25.0 [22.4; 28.8]	-2.433	0.012*	14.8 [8.7; 19.2]	16.0 [8.9; 21.5]	-0.356	0.758	3.1 [1.9; 7.2]	0.3 [-1.5; 1.8]	28.000	0.034*	0.88
5-STS (s)	9.4 [6.9; 13.0]	9.3 [6.0; 14.0]	-1.804	0.077	7.6 [5.6; 9.8]	7.0 [5.7; 7.9]	-1.542	0.148	-0.9 [-2.0; 0.1]	-0.8 [-2.5; 0.8]	46.000	0.893	0.00
CAT total score	23.0 [19.3; 24.8]	14.5 [6.3; 19.5]	-2.983	0.001*	21.0 [14.0; 28.0]	23.0 [11.0; 30.0]	-0.614	0.572	-6.0 [-15.0; -4.0]	0.0 [-8.0; 3.0]	26.500	0.013*	-1.10

Values are presented as median [interquartile range], unless otherwise stated. *p<0.05

Legend: 5-STS, 5-repetitions sit-to-stand test; bpm, beats per minute; CAT, COPD assessment test; cpm, cycles per minute; Diff CG, pre/post difference in the control group; Diff EG, pre/post difference in the experimental group; ES, effect size; mBorg, modified Borg scale; mMRC, modified British Medical Research Council questionnaire; QMS, quadriceps muscle strength; SpO_2, peripheral oxygen saturation.

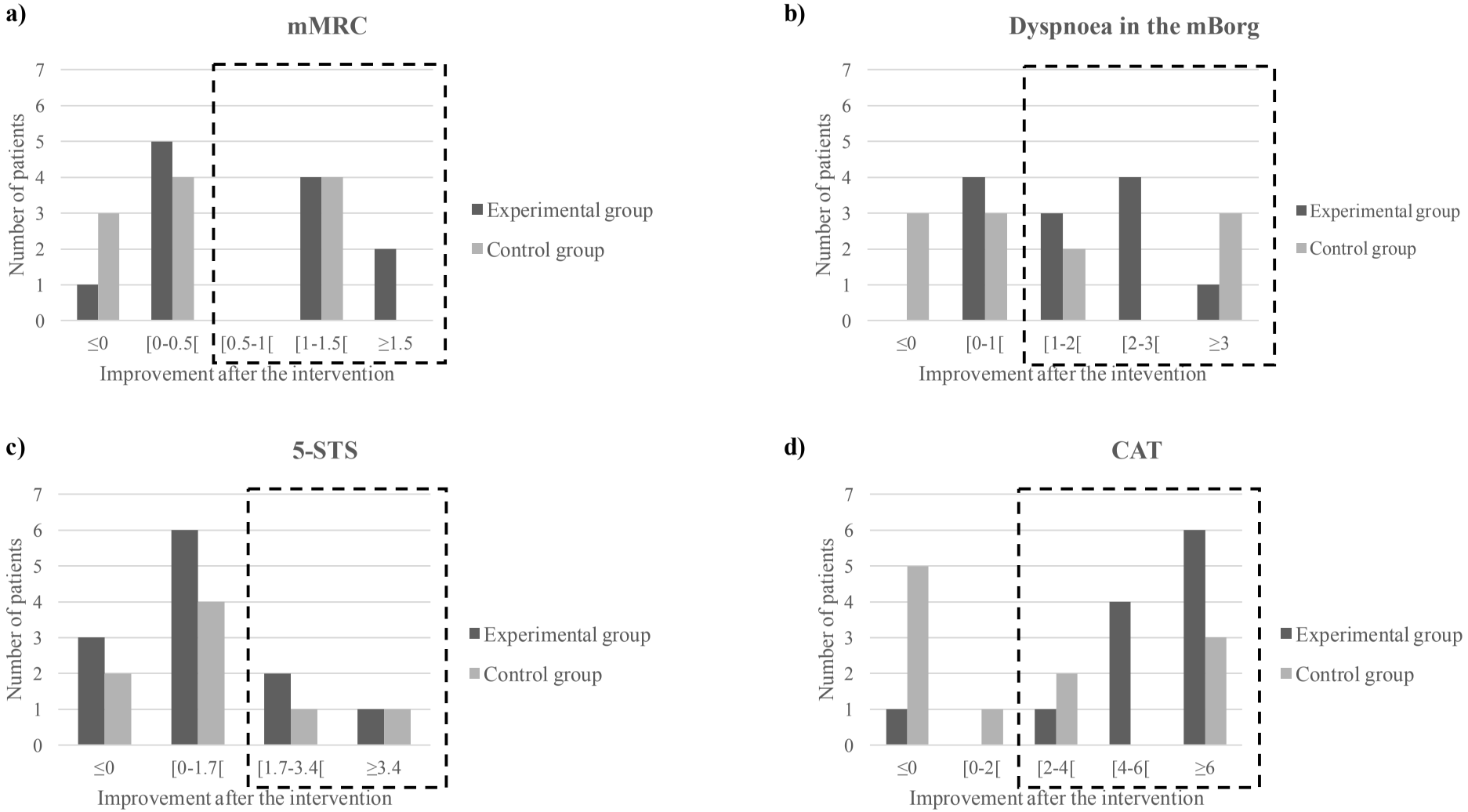

Figure 2 – Distribution of the level of improvement after the intervention in: **a)** the modified British Medical Research Council dyspnoea questionnaire (mMRC); **b)** symptoms of dyspnoea in the modified Borg scale (mBorg); **c)** the 5-repetition sit-to-stand test (5-STS); and **d)** the COPD assessment test (CAT) total score. Dotted line indicates the number of patients that improved above the minimal clinically important difference for each measure, i.e., mMRC – 0.5 units, mBorg – 1 unit, 5STS – 1.7s and CAT – 2 units.

4. Discussion

This pilot study showed that community-based PR is safe and effective during AECOPD. Significant improvements were found on symptoms, vital signs, impact of the disease and quadriceps muscle strength.

Symptoms, particularly dyspnoea, are a key feature of AECOPD (Haughney et al., 2005) and have been considered important outcomes of PR during this period of the disease (Puhan et al., 2016), as it is known that even small improvements on dyspnoea are valued by patients (Haughney et al., 2005). Although often ignored, fatigue is presented in 50-70% of patients with COPD and is usually increased in AECOPD, highlighting the importance of assessing this symptom as well (Spruit, Vercoulen, Sprangers, & Wouters, 2017). In fact, in this study, after PR, a moderate effect size was found for fatigue in the mBorg and most of the patients improved their dyspnoea above the MCID in the mMRC and in the mBorg. Nevertheless, these results must be carefully interpreted as dyspnoea and fatigue are multifactorial symptoms and the mBorg is an unidimensional tool that assesses only the specific moment at which is used (Bausewein, Farquhar, Booth, Gysels, & Higginson, 2007). Multidimensional and disease-specific scales, such as the baseline/transition dyspnoea index and the multidimensional fatigue index, allow a multifactorial assessment of these symptoms and might contribute to a better understanding of their behaviour during the course of a PR programme in AECOPD (Bausewein et al., 2007; Breslin et al., 1998). Moreover, the MCID for the mMRC and the mBorg has been established for patients with AECOPD receiving just standard of care (Oliveira et al., 2017), thus it is likely that different MCID established specifically to PR during AECOPD will become available in the future (Oliveira & Marques, 2017).

Despite the importance of assessing individual symptoms, it is known that is the combination of all symptoms what really impacts on patients' health-related quality of life (Oliveira & Marques, 2017), being the overall impact of the disease one of the outcomes that most concern patients during AECOPD (Haughney et al., 2005). These reasons demand a comprehensive symptom assessment (The Global Initiative for Chronic Obstructive Lung Disease, 2018). CAT is a multidimensional questionnaire that has been developed to cover the most burdensome symptoms and limitations perceived by patients with COPD, and recent literature has advocating its use to assess PR during AECOPD (Oliveira & Marques, 2017). In this study, the significant improvements accompanied by large effect sizes found after PR, and the number of patients improving above the MCID, show that CAT is sensitive to changes after PR and is able to capture its benefits during AECOPD, supporting its use in clinical practice.

Heart rate, respiratory rate and SpO_2 have been previously assessed in PR programmes conducted in hospitalised patients with AECOPD and improvements, or patterns of improvement, have been reported (Ali, Talwar, & Jain, 2014; Eaton et al., 2009; Kirsten, Taube, Lehnigk, Jörres, & Magnussen, 1998; Murphy, Bell, & Costello, 2005), suggesting that PR is a safe approach during AECOPD. The results from this pilot study also corroborate these findings for community-based PR and add that no adverse events were reported. However, a careful interpretation of this finding is needed as a systematically assessment of adverse events was not conducted. Future studies should carefully assess occurrence of adverse events and need for unscheduled health care visits during and after each session of PR to establish effectiveness and safeness of community-based PR during AECOPD.

Peripheral muscle weakness, particularly of quadriceps, is a well-known key systemic consequence of COPD (The Global Initiative for Chronic Obstructive Lung Disease, 2018) that affects patients' physical activity, exercise tolerance, health-related quality of life and survival (Maltais et al., 2014). During AECOPD there is an even more accentuated decline in muscle function, resulting in long-term losses on functional capacity (Troosters et al., 2010). Since limb muscle dysfunction can be prevented and improved (Maltais et al., 2014), and PR has been shown to increase quadriceps muscle strength in this and previous studies (Seymour et al., 2010; Tang, Blackstock, Clarence, & Taylor, 2012; Torres-Sánchez et al., 2016), it seems imperative to consider PR during AECOPD as a strategy to manage peripheral muscle weakness and prevent further clinical declines.

It has been recognised that functionality, a vital outcome for patients' daily life, is severely impaired during AECOPD (Chin, 2017; Haughney et al., 2005). In this study, no differences were found in patients' functionality after PR, however this is more probably due to the lack of sensitive to change of the measure used than to an ineffectiveness of the intervention, since a ceiling effect was observed in the 5-STS. In fact, in the baseline assessment patients already presented a relatively good functional status as they were below the cut off for risk of falling, hence, they had no room for improvement. Given the importance of this outcome, further research on the most appropriate outcome measure to assess functionality in patients with AECOPD is needed. Step tests, gait speed tests, tests based on activities of daily living, longer sit-to-stand tests (such as the 30-seconds or the 1-minute sit-to-stand tests) and the short physical performance battery could be possible alternatives (Lee, Harrison, Beauchamp, Janaudis-Ferreira, & Brooks, 2015; Maddocks, Nolan, & Man, 2017; Vaidya, Chambellan, & de Bisschop, 2017; Volpato et al., 2010). Since the short physical performance battery i) is a more comprehensive tool than the others referred before; ii) has shown to be valid and simple to detect patients with COPD with functional impairments; and iii) has been used to assess

hospitalised patients, namely with AECOPD, being related with the risk of re-hospitalisation and death (Patel et al., 2014; Volpato et al., 2010), it seems the most promising measure to assess patients with AECOPD managed on an outpatient basis.

In sum, significant improvements in well-established outcomes of PR, that are usually associated with an increased risk of AECOPD and poor prognosis, were found and no adverse events were reported. Therefore, community-based PR seems a promising, safe and feasible approach to provide a timely and effective management of patients with AECOPD, which is crucial to reduce hospital admissions and recovery time whilst improving patients' health-related quality of life. Moreover, community-based PR responds to a national and international priority of increasing patients' access to PR (Diário da República, 2016; Simão & Almeida, 2009; Spruit et al., 2013; The Global Initiative for Chronic Obstructive Lung Disease, 2018).

Nevertheless, some limitations need to be acknowledged. Firstly, this study was not randomised nor blinded, which could have biased the results. However, efforts were made to minimise this risk by implementing a well-defined assessment protocol and intervention. Since informative and promising results were obtained, a more robust methodology is now required. Randomised studies, with larger samples and blind assessors are warranted. These are fundamental to clarify the role of community-based PR in AECOPD. Secondly, exercise capacity which is a key outcome of PR for stable patients, was not assessed in this study due to lack of space to perform the assessment, although aerobic training has been performed. Thus, future studies should explore the effects of community-based PR during AECOPD on patients' exercise capacity using alternative field-tests which are able to assess patient' exercise capacity. Thirdly, the long-term effects of the community-based PR programme were not assessed due to the limited time available to conduct this study. Given the known long-term consequences of AECOPD on patients' health status and disease progression, a careful assessment of the long-term effects of PR during AECOPD is needed.

5. Conclusions

This pilot study showed that community-based PR programmes during AECOPD are safe and provide similar benefits to those well-established for PR in stable COPD. The addition of PR to standard of care in the management of AECOPD resulted in important improvements on respiratory rate, symptoms, quadriceps muscle strength and impact of the disease, parameters usually associated with an increased risk of AECOPD and poor prognosis. Future research with a more robust methodology is now required to clarify the role of community-based PR in AECOPD.

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Appendix 1 – List of publications developed under the scope of this dissertation

1. Machado Ana, Silva Pedro, Afreixo Vera, Marques Alda (2018) "Design of pulmonary rehabilitation programs during acute exacerbations of COPD: a systematic review and meta-analysis". Chest. (Fator de Impacto 6.147; FI 5 anos 7.327) RESPIRATORY SYSTEM: Q1, CRITICAL CARE MEDICINE: Q1 (submitted)
2. Machado Ana, Oliveira Ana, Valente Carla, Burtin Chris, Marques Alda (2018) "Community-based pulmonary rehabilitation during acute exacerbations of COPD". 28th European Respiratory Society (ERS) International Congress, 15-19th September 2018, Paris, France (accepted as poster discussion)
3. Machado Ana, Silva Pedro, Marques Alda (2018) "Design of pulmonary rehabilitation during acute exacerbations of COPD". 28th European Respiratory Society (ERS) International Congress, 15-19th September 2018, Paris, France (accepted as poster discussion)
4. Machado Ana, Miranda Sara, Oliveira Ana, Melro Hélder, Marques Alda (2017) "Efeitos da Reabilitação Respiratória nas Exacerbações Agudas da Doença Pulmonar Obstrutiva Crónica". Proceedings of the 10th Congresso Nacional de Fisioterapeutas; p. 18; ISBN: 978-972- 96015-1- 4 (oral communication)
5. Machado Ana, Oliveira Ana, Paixão Cátia, Miranda Sara, Melro Hélder, Ferreira Diva, Marques Alda (2017) "Rehabilitation effects on computerized respiratory sounds of patients with AECOPD". Proceedings of the 42nd Annual Conference of the International Lung Sounds Association; 182:58-59. ISBN: 978-82-8378-003-1 (oral communication)