University of Porto Faculty of Sport Research Center in Physical Activity, Health and Leisure

# Pulmonary rehabilitation in mild chronic obstructive pulmonary disease and its impact on computerized respiratory sounds

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PALAVRAS-CHAVE: CHRONIC OBSTRUCTIVE PULMONARY DISEASE, MILD CHRONIC OBSTRUCTIVE PULMONARY DISEASE, PULMONARY REHABILITATION, COMPUTERIZED AUSCULTATION, RESPIRATORY SOUNDS.

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The best preparation for tomorrow is doing your best today.

H. Jackson Brown, Jr.

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#### Resumo

Embora a reabilitação respiratória (RR) seja uma intervenção baseada na evidência para pacientes com doença pulmonar obstrutiva crónica (DPOC), esta Tese focou-se em duas áreas onde alguma incerteza subsiste. Em primeiro lugar, a RR tem apenas uma recomendação fraca para pacientes com um volume expiratório máximo no 1º segundo (VEMS) superior a 50% do previsto, e por isso a efetividade desta intervenção em pacientes com DPOC ligeira necessita ser investigada. A revisão sistemática I desta Tese sintetizou a literatura existente nesta área. Em segundo lugar, com base no VEMS, tem sido preconizado que a RR não melhora a função pulmonar na DPOC. No entanto, o VEMS reflete principalmente alterações nas vias aéreas superiores, apesar de ser reconhecido que a DPOC afeta primariamente as vias aéreas inferiores. Assim, existe a necessidade de explorar os efeitos da RR na função pulmonar e os sons respiratórios computorizados podem ser uma medida inovadora para explorar esta área (revisão sistemática II). Os estudos originais I e II desta Tese mostraram que a RR é viável e benéfica para pacientes com DPOC ligeira. Estes estudos também demonstraram que, à semelhança do que se observa na DPOC moderada a grave, os benefícios declinam com o tempo. O estudo III verificou que os sons respiratórios computorizados em pacientes com DPOC são fiáveis a um fluxo de ar de 0.4-0.6 L/s. Os estudos IV e V demonstraram que os sons respiratórios computorizados são sensíveis a mudanças na função pulmonar devido a exacerbações agudas da doença e à RR. Estes resultados constituem nova evidência na efetividade de RR na DPOC ligeira e no campo emergente da auscultação computorizada. O papel da RR na trajetória da DPOC ligeira e o potencial dos sons respiratórios computorizados como medida de resultado são tópicos de investigação que requerem mais atenção num futuro próximo.

Palavras-chave: DOENÇA PULMONAR OBSTRUTIVA CRÓNICA, DOENÇA PULMONAR OBSTRUTIVA CRÓNICA LIGEIRA, REABILITAÇÃO RESPIRATÓRIA, AUSCULTAÇÃO COMPUTORIZADA, SONS RESPIRATÓRIOS.

#### Abstract

Even though pulmonary rehabilitation (PR) is an evidence-based intervention for patients with chronic obstructive pulmonary disease (COPD), this Thesis has focused on two areas where uncertainty remains. Firstly, PR is only weakly recommended for patients with a forced expiratory volume in 1 second (FEV<sub>1</sub>) greater than 50% predicted, thus the effectiveness of this intervention in patients with mild disease needs to be investigated. The systematic review I of this Thesis synthetized the literature in this area. Secondly, based on FEV<sub>1</sub>, it has been accepted that PR does not improve lung function in COPD. However, FEV1 mainly reflects structural changes in the large airways and it is well-recognized that COPD primarily targets small airways. Hence, there is a need to explore the effects of PR on lung function and computerized respiratory sounds can be a novel outcome measure to explore this area (systematic review II). The original studies I and II of this Thesis showed that PR is feasible and beneficial for patients with mild COPD. These studies also demonstrated that, similarly to what happens in moderate-to-severe COPD, the benefits decline overtime. Study III found that computerized respiratory sound parameters in patients with COPD are reliable at an airflow of 0.4-0.6 L/s. Studies IV and V showed that computerized respiratory sounds are sensitive to lung function changes due to acute exacerbations of the disease and PR. These findings constitute new evidence on the effectiveness of PR in mild COPD and on the emerging field of computerized auscultation. The role of PR in mild COPD trajectory and on the potential of computerized respiratory sounds as a surrogate outcome measure are research topics requiring further attention in the near future.

Key words: CHRONIC OBSTRUCTIVE PULMONARY DISEASE, MILD CHRONIC OBSTRUCTIVE PULMONARY DISEASE, PULMONARY REHABILITATION, COMPUTERIZED AUSCULTATION, RESPIRATORY SOUNDS.

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## List of abbreviations and symbols

10-RM	10-repetition maximum
1-RM	1-repetition maximum
2CD	Two cycle duration
6MWD	6-min walk distance
6MWT	6-min walk test
AECOPD	Acute exacerbation of chronic obstructive pulmonary disease
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CORSA	Computerized Respiratory Sound Analysis
CRS	Computerized Respiratory Sounds
DASS	Depression, Anxiety, Stress Scales
ES	Effect size
F50	Median frequency
FEV <sub>1</sub>	Forced expiratory volume in 1 second
FFT	Fast Fourier Transform
FVC	Forced vital capacity
GOLD	Global initiative for chronic Obstructive Lung Disease
HRQOL	Health-related quality of life
ICC	Intraclass correlation coefficient
IDW	Initial deflection width
К	Cohen's kappa
Kendall's W	Kendall's coefficient of concordance

MD	Mean difference
mMRC	Modified Medical Research Council questionnaire
NRS	Normal respiratory sounds
η²	Partial eta-squared
Ρ	p-value
PICO	Population, Intervention, Comparison and Outcome
PR	Pulmonary rehabilitation
PRISMA	Preferred reporting items for systematic reviews and meta-
	analyses
R	Effect size for Mann–Whitney U-tests
RCT	Randomized controlled trial
<b>r</b> p	Pearson's coefficient
ſs	Spearman's rho
RS	Respiratory sounds
SGRQ	St George Respiratory Questionnaire
VT	Tidal volume
WHO	World Health Organization
α	alpha

Chapter I

Introduction

#### **General Introduction**

Chronic respiratory diseases, defined as chronic diseases of the airways and other structures of the lungs, represent a major health, societal and economic burden worldwide (World Health Organization [WHO], 2007). More than 1 billion people suffer from chronic respiratory diseases (Forum of International Respiratory Societies, 2013) and, in Europe, the total annual cost of respiratory diseases amounts to more than €380 billion (European Respiratory Society, 2013a). Chronic obstructive pulmonary disease (COPD), together with asthma, lung cancer, acute respiratory infections and tuberculosis, are the five major respiratory diseases contributing for a great burden to society (Forum of International Respiratory Societies, 2013).

COPD affects 210 million people worldwide (WHO, 2007) and 800.000 people in Portugal (Bárbara et al., 2013; Observatório Nacional das Doenças Respiratórias, 2011). Moreover, it is known that its prevalence is increasing (Mehrotra, Oluwole, & Gordon, 2009; Menezes et al., 2005). In the United States of America, between 1969 and 2013, an overall decreasing trend in agestandardized death rate was observed for leading chronic diseases, such as heart disease, cancer, stroke and diabetes, while the death rate for COPD increased (Ma, Ward, Siegel, & Jemal, 2015). The disease burden is also increasing, and in 2013 COPD was considered the 8<sup>th</sup> cause of global years lived with disability (Vos et al., 2015). These epidemiologic data indicate that COPD will pose tremendous challenges for health care systems and societies in the next decades.

According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD), COPD is a preventable and treatable disease characterized by a persistent airflow limitation (GOLD, 2016). The airflow limitation, determined by the fixed ratio, post-broncodilator forced expiratory volume in 1 second (FEV<sub>1</sub>)/forced vital capacity < 0.70, is *"usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases"* (GOLD, 2016). The respiratory manifestations of the

disease range from dyspnea, chronic cough, sputum production and wheezing to recurrent respiratory infections and respiratory failure (Barnes & Celli, 2009; Pauwels & Rabe, 2004; Voll-Aanerud, Eagan, Wentzel-Larsen, Gulsvik, & Bakke, 2008). However, the pathogenesis and clinical features of COPD are also associated with systemic manifestations such as cardiovascular compromise, muscle weakness, weight loss, osteoporosis, anemia, diabetes, depression and anxiety (Barnes & Celli, 2009; Seymour et al., 2010; Sinden & Stockley, 2010; Wouters, Creutzberg, & Schols, 2002). Accordingly, the goals of COPD treatment are to reduce long-term lung function decline, relieve symptoms, improve exercise tolerance and health-related quality of life, prevent complications and exacerbations; and reduce hospitalizations and mortality (European Respiratory Society, 2013b; Qaseem et al., 2011). To address these multiple goals, the main COPD management strategies are inhaled therapies, supplemental oxygen therapy and pulmonary rehabilitation programs (Qaseem et al., 2011).

Pulmonary rehabilitation is defined as "a comprehensive intervention based on a thorough patient assessment followed by patient tailored therapies that include, but are not limited to, exercise training, education, and behavior change, designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence to health-enhancing behaviors" (Spruit et al., 2013). The main goals of this comprehensive intervention are minimize symptom burden, maximize exercise performance, promote autonomy, increase participation in everyday activities, enhance health-related quality of life, and effect long-term health-enhancing behavior change (Spruit et al., 2013).

Although pulmonary rehabilitation is a relatively recent practice in respiratory medicine (European Respiratory Society, 2013b), it is currently considered a core component of the integrated care of patients with COPD (Nici & ZuWallack, 2012). Its meteoric rise in acceptance is due to the fact that there is a sound evidence base showing its benefits (Boxall, Barclay, Sayers, & Caplan, 2005; Ergun et al., 2011; Griffiths et al., 2000; Troosters, Gosselink, & Decramer,

2000). Improvements on exercise capacity and health-related quality of life; reduction in dyspnea, in anxiety and depression symptoms and in the number of hospitalizations are some of the described benefits with higher level of evidence (Evidence A and B) (Bolton et al., 2013; GOLD, 2016). In addition, pulmonary rehabilitation covers a range of non-pulmonary features, such as muscle weakness, depression and anxiety (Paz-Díaz, Montes de Oca, López, & Celli, 2007; Troosters et al., 2000), that may not be adequately addressed by other COPD management strategies (GOLD, 2016).

Even though pulmonary rehabilitation is a generally accepted evidencebased treatment modality for patients with COPD (Bolton et al., 2013; GOLD, 2016; Spruit et al., 2013), a number of areas that warrant further investigation can be identified. This Thesis provides contributes for two of them. Firstly, based on the limited evidence available, pulmonary rehabilitation is only weakly recommended for patients with mild-to-moderate COPD (Qaseem et al., 2011). Therefore, evidence on the effectiveness of pulmonary rehabilitation in patients with mild disease is needed (Research question 1). Secondly, based on FEV<sub>1</sub>, the globally established outcome for lung function, it has been generally accepted that pulmonary rehabilitation does not improve lung function in COPD (Spruit et al., 2013). Nevertheless, FEV<sub>1</sub> mainly reflects structural changes in the large airways (Annesi et al., 1992; Cohen et al., 2007; McNulty & Usmani, 2014), while COPD pathogenesis primarily targets small airways (Gelb et al., 1996; GOLD, 2016; Hogg et al., 2004). Thus, the effects of pulmonary rehabilitation on lung function should be investigated, and computerized respiratory sounds can be a novel outcome measure to explore this area of knowledge (Research question 2). The rational underpinning these two research questions are described in detailed below.

The work developed is presented in five chapters. An introduction to the Thesis (**Chapter I**) is first provided with an overview of the two research questions and research objectives. This chapter is followed by **Chapter II** – background, where two systematic reviews are presented. **Systematic review I** presents a

review of the evidence concerning the impact of pulmonary rehabilitation in patients with mild COPD, and Systematic review II summarizes the existing evidence on computerized respiratory sounds in patients with COPD. Chapter III is composed of five original studies developed to address the two research questions within the timeframe of this Thesis. Research question 1 starts to be addressed in Study I, where a pretest-posttest study evaluating the impact of pulmonary rehabilitation in patients with mild COPD was conducted. Study II builds further on the observations of Study I and explored both short- and longterm effects of pulmonary rehabilitation in patients with mild COPD in comparison with patients with moderate-to-severe COPD. Research question 2 starts to be addressed in Study III, where reliability of computerized respiratory sounds in patients with COPD is reported. **Study IV** explored differences in computerized respiratory sounds between patients with stable COPD and patients with acute exacerbation of COPD and Study V evaluated the short- and mid-term effects of pulmonary rehabilitation on computerized respiratory sounds in patients with COPD. An integrated discussion of the main findings, overall limitations and implications for future research and clinical practice follows in **Chapter IV**. Finally, **Chapter V** outlines the main conclusions. Figure 1 provides a graphic presentation with the rationale of this Thesis.



Figure 1. Graphic presentation explaining the rationale of this Thesis

#### **Research question 1**

The severity of COPD has been traditionally based on the airflow limitation, specifically, on the FEV<sub>1</sub> (GOLD, 2016). The GOLD spirometric classification is divided in four grades: mild,  $FEV_1 \ge 80\%$  of the predicted; moderate,  $50\% \le FEV_1 < 80\%$  of the predicted; severe,  $30\% \le FEV_1 < 50\%$  of the predicted, and very severe,  $FEV_1 < 30\%$  of the predicted (GOLD, 2016).

To date, the largest proportion of evidence on the clinical characteristics and management of COPD has focused on patients with moderate-to-verysevere disease. This may be attributed to two main factors. On the one hand, these patients are generally more impaired and generate higher medical costs than patients with less severe airflow (Miravitlles, Murio, Guerrero, & Gisbert, 2003; Seymour et al., 2010). On the other hand, COPD remains largely underdiagnosed, and less severe airflow limitation has been associated with higher probability of underdiagnosis (Kart et al., 2014; Lamprecht et al., 2015).

Mild COPD is, nevertheless, one of the most prevalent grades of the disease (Menezes et al., 2005) and also places a substantial burden on health care systems, with costs ranging from €1168 to €1286 per patient/year (Hilleman, Dewan, Malesker, & Friedman, 2000; Miravitlles et al., 2003). More importantly, evidence have showed that physical activity levels, quadriceps muscle strength and health-related quality of life are already impaired in patients with mild COPD (Maltais, Dennis, & Chan, 2013; Shrikrishna et al., 2012; Troosters et al., 2010) and that these impairments worsen over time (Maltais et al., 2013). COPD, independently of its severity, impacts on patients as well as on health care systems (Hilleman et al., 2000; Miravitlles et al., 2003). Therefore, it is imperative to plan health care for patients with COPD at all grades.

A meta-analysis conducted by Lacasse et al. (2006) established that pulmonary rehabilitation is effective in relieving dyspnea and fatigue and in improving health-related quality of life in patients with COPD. However, in this meta-analysis only patients with moderate, severe and very severe COPD were analyzed (Lacasse et al., 2006). Based on the available evidence, pulmonary rehabilitation is a recognized intervention in patients with COPD, but patients are generally not referred to pulmonary rehabilitation programs until they have advanced COPD (Spruit et al., 2013).

According to the GOLD, pulmonary rehabilitation should be offered to patients who feel dyspnea when walking on their own pace on level ground (GOLD, 2016). A clinical practice guideline endorsed by the American College of Physicians, the American College of Chest Physicians, the American Thoracic Society and the European Respiratory Society strongly recommend that pulmonary rehabilitation should be prescribed for symptomatic patients with a FEV<sub>1</sub> of less than 50% of the predicted (Qaseem et al., 2011). The prescription

of pulmonary rehabilitation for symptomatic or exercise-limited individuals with a FEV<sub>1</sub> greater than 50% of the predicted has only a weak recommendation (Qaseem et al., 2011). Based on the lack of recommendation of pulmonary rehabilitation in patients with mild COPD, the standard care of patients with mild COPD typically includes encouragement of risk factor avoidance, advise to increase physical activity and pharmacological therapy (GOLD, 2016).

As COPD is a complex and progressive disease, referral to pulmonary rehabilitation at an earlier stage would allow for more emphasis on preventive strategies, maintenance of physical activity and possibly in delaying the decline of lung function (Spruit et al., 2013). Hence, the disease-modifying potential of pulmonary rehabilitation in patients with mild COPD should be investigated. This has been identified as a major research topic by the latest American Thoracic Society/European Respiratory Society official statement on pulmonary rehabilitation (Spruit et al., 2013). Aiming at contributing for the development of this important area of research, **Systematic review I** summarized the evidence concerning the impact of pulmonary rehabilitation in patients with mild COPD. It comprehensively describes and discusses the impact of pulmonary rehabilitation on exercise tolerance, health-related quality of life, use of health care resources and lung function in patients with mild COPD.

A preliminary study from Riario-Sforza et al. (2009) found that, after a 6week pulmonary rehabilitation program, patients with mild COPD improved their exercise tolerance. However, the effects of pulmonary rehabilitation on other health domains were not explored. In line with the research conducted in more severe grades of COPD, it is hypothesized that patients with mild COPD will also benefit from pulmonary rehabilitation and that these benefits will be observed in different health domains. **Study I** provides the results of a quasi-experimental one group pretest-posttest study evaluating the impact of pulmonary rehabilitation on lung function, dyspnea, functional balance, muscle strength, exercise tolerance, emotional state and health-related quality of life of patients with mild COPD.

Pulmonary rehabilitation appears to improve exercise tolerance and health-related quality of life in patients with mild COPD (Liu et al., 2012; Riario-Sforza et al., 2009). However, these observations are based in studies investigating only the short-term effects of pulmonary rehabilitation. Nevertheless, one of the major goals of pulmonary rehabilitation is to promote the long-term adherence of health-enhancing behaviors, such as adherence to medication, regular exercise, healthy nutritional habits, breathing techniques, energy-saving strategies during activities of daily living (Velloso & Jardim, 2006), and maintenance of benefits (Spruit et al., 2013). In patients with moderate-tovery-severe COPD, it is well known that in the absence of any maintenance strategy, benefits of pulmonary rehabilitation diminish over 6-12 months (Griffiths et al., 2000; Spruit, Troosters, Trappenburg, Decramer, & Gosselink, 2004). A number of reasons explain this long-term decline: decreased adherence to regular exercise, progression of the disease, occurrence of comorbidities and exacerbations (Bestall et al., 2003; Foglio et al., 2007; Heppner, Morgan, Kaplan, & Ries, 2006). It is hypothesized that patients with mild COPD may benefit equally from pulmonary rehabilitation and its benefits may also decrease over time. Study II builds further on the observations in Study I and explores both the shortand long-term effects of pulmonary rehabilitation in patients with mild COPD in comparison with patients with moderate-to-severe COPD.

#### **Research question 2**

The pathophysiological basis of COPD is the presence of airflow limitation, which originates specific respiratory manifestations, as described earlier in this Thesis. However, COPD is also well recognized by its systemic consequences, such as poor exercise tolerance, muscle weakness, weight loss and comorbidities (Barnes & Celli, 2009; Seymour et al., 2010; Sinden & Stockley, 2010; Wouters et al., 2002). COPD is, therefore, characterized by several different clinical features and no single outcome can capture the variety of pathological effects or assess the effectiveness of therapeutic interventions (Jones & Agusti, 2006).

Taking into consideration this heterogeneity, the latest American Thoracic Society/European Respiratory Society research statement in COPD recognized that there is increasing emphasis on using patient-centered outcomes (i.e., outcomes that matter to patients) in clinical research and supported their use to inform judgments related to patient care (Celli et al., 2015). It also recommended the identification of high-quality surrogate outcomes (i.e., outcomes that represent physiological and/or anatomical processes). These outcomes have the advantages of being readily measured, providing information about the disease progression and at the same time making research easier, more efficient and less costly (Celli et al., 2015; Wilt et al., 2012). Hence, according to this statement, the effectiveness of interventions in COPD should be established using both patientcentered and surrogate outcomes.

In the case of pulmonary rehabilitation, patient-centered outcomes, namely health-related quality of life, exercise capacity and dyspnea, have been identified as the most important outcomes (Spruit et al., 2014). Surrogate outcomes, such as rectus femoris cross-sectional area, fat-free mass, C-reactive protein and FEV<sub>1</sub>, have also been used to assess the effects of pulmonary rehabilitation (Camp, Appleton, & Reid, 2000; Jones & Agusti, 2006; Menon et al., 2012; Sugawara et al., 2010; van Wetering, Hoogendoorn, Mol, Rutten-van Molken, & Schols, 2010). FEV<sub>1</sub> has been established as the global surrogate marker for COPD diagnosis and monitoring (GOLD, 2016). However, unlike the other outcomes, FEV<sub>1</sub> has not been found to be responsive to pulmonary rehabilitation (Camp et al., 2000; Niederman et al., 1991; Ries, Kaplan, Limberg, & Prewitt, 1995).

Considering this evidence, and in the absence of other globally accepted surrogate outcome for lung function, it has been generally accepted that pulmonary rehabilitation does not improve lung function in COPD (Spruit et al., 2013). Nevertheless, FEV<sub>1</sub> mainly reflects structural changes in the large airways (Annesi et al., 1992; Cohen et al., 2007; McNulty & Usmani, 2014) and it is well-recognized that COPD primarily targets small airways (Gelb et al., 1996; GOLD,

2016; Hogg et al., 2004). In addition, as pointed out by Jones and Agusti (2006), the traditional use of FEV<sub>1</sub> to assess treatment effectiveness is paradoxical, since COPD is diagnosed on the basis of a poorly responsive FEV<sub>1</sub> to bronchodilator therapy. Hence, there is a need to explore new surrogate outcomes to assess the effects of pulmonary rehabilitation on lung function. These outcomes should be simple in terms of measurement, interpretation and resources used, and have acceptable reliability (Jones & Agusti, 2006).

Computerized respiratory sounds are a simple, objective and non-invasive surrogate measure to assess the function of the respiratory system (Bohadana, Izbicki, & Kraman, 2014). Computerized respiratory sounds can be obtained through computerized auscultation, which consists of recording patients' respiratory sounds with an electronic device and classifying/analyzing them based on specific signal characteristics (Kandaswamy, Kumar, Ramanathan, Jayaraman, & Malmurugan, 2004; Moussavi, Leopando, Pasterkamp, & Rempel, 2000; Polat & Guler, 2004). Thus, computerized respiratory sounds do not require special resources beyond those typical of a patient-health professional encounter.

Computerized respiratory sounds can be divided in two main types, normal and adventitious sounds (Sovijärvi et al., 2000). Normal respiratory sounds are "the sound arising from breathing, heard or recorded over the chest wall, the trachea or at the mouth" (Sovijärvi et al., 2000). These sounds are generated by the airflow in the respiratory tract and characterized by broad spectrum noise (Sovijärvi et al., 2000). Adventitious respiratory sounds are additional sounds superimposed on normal respiratory sounds, which can be continuous (wheezes) or discontinuous (crackles) (Sovijärvi et al., 2000). Wheezes have a musical character (dominant frequency usually over 100 Hz), while crackles are explosive sounds (Sovijärvi et al., 2000). The presence of adventitious sounds usually indicates a pulmonary disorder (Sovijärvi et al., 2000). Both normal and adventitious respiratory sounds have been found to be directly related to movement of air, changes within lung morphology and presence of secretions
(Bohadana et al., 2014; Kiyokawa & Pasterkamp, 2002). The advent of computerized respiratory sounds may enable COPD research to move beyond FEV<sub>1</sub> by providing quantitative information on lung function and detecting significant responses to therapy.

The analysis of computerized respiratory sounds alone is, however, insufficient to improve the diagnostic and monitoring of patients with COPD. Even with an objective method, health professionals cannot interpret with confidence the findings on computerized respiratory sounds, without a clear definition of what are the typical auscultation findings in patients with COPD during stable periods. Thus, Systematic review II reviewed the existing evidence on computerized respiratory sounds in stable COPD. This review highlighted the major gaps in the literature and the areas where further original research is required. In addition, this work underlined the nonexistence of studies about the reliability of computerized respiratory sounds in COPD. Acceptable reliability is an essential property of any outcome measure, ensuring that the error involved in measurement is small enough to detect actual changes (Jones & Agusti, 2006; Kottner et al., 2011). This gap in the literature hinders the interpretation of actual changes in computerized respiratory sounds. To address this relevant research need, in **Study III** the reliability of computerized respiratory sounds in patients with COPD was investigated.

Computerized respiratory sounds with abnormal characteristics have provided objective evidence of COPD in 14 patients with a history compatible with the disease, but not detectable by spirometry (Gavriely, Nissan, Cugell, & Rubin, 1994). In patients with COPD, it has also been shown that the number of detected wheezes, as well as their frequency, during forced expiratory maneuvers decreased after inhalation of a bronchodilator (Fiz et al., 2002). In addition, it has been demonstrated that it is possible to characterize the course of acute exacerbations of COPD in two different respiratory sound patterns based on the variation of spectral parameters (Sánchez Morillo, Astorga Moreno, Fernández Granero, & León Jiménez, 2013). From the available evidence, it appears that computerized respiratory sounds provide valuable information regarding the respiratory system and may have the potential to detect changes in lung function due to an acute exacerbation of COPD or after pulmonary rehabilitation. However, to date, there are no studies exploring if computerized respiratory sounds differ significantly between stable and exacerbation periods in COPD or change with pulmonary rehabilitation. **Study IV** explores differences in computerized respiratory sounds between patients with stable COPD and patients with acute exacerbation of COPD and **Study V** evaluates the short- and mid-term effects of pulmonary rehabilitation on computerized respiratory sounds in patients with COPD.

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Chapter II

Background

Systematic review I

# Pulmonary rehabilitation for mild COPD: a systematic review

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# Abstract

**Background:** Pulmonary Rehabilitation (PR) is effective in improving exercise capacity and health-related quality of life (HRQOL) in patients with moderate-to-very-severe COPD. Quadriceps strength and HRQOL can be impaired in patients with mild COPD, therefore, patients at this grade may already benefit from PR. However, the impact of PR in mild COPD remains unestablished. Thus, this systematic review assessed the impact of PR on exercise capacity, HRQOL, health-care resource use and lung function in patients with mild COPD.

**Methods:** The Web of knowledge, EBSCO, MEDLINE and SCOPUS databases were searched up to April 2013. Reviewers independently selected studies according to the eligibility criteria.

**Results:** Three studies with different designs (retrospective, one group pretest-posttest, and randomized controlled trial) were included. Out-patient PR programs were implemented in two studies, which included mainly aerobic, strength, and respiratory muscle training. The randomized controlled trial compared a PR home-based program, consisting of 6 months of walking and participating in ball game games, with standard medical treatment. Significant improvements in exercise capacity (effect size [ES] 0.87-1.82) and HRQOL (ES 0.24-0.86) were found when comparing pretest-posttest data and when comparing PR with standard medical treatment. In one study, a significant decrease in hospitalization days was found (ES 0.38). No significant effects were observed on the number of emergency department visits (ES 0.32), number of hospitalizations (ES 0.219) or lung function (ES 0.198).

**Conclusions:** Most of the PR programs had significant positive effects on exercise capacity and HRQOL in patients with mild COPD; however, their effects on health-care resource use and lung function were inconclusive. This systematic review suggests that patients with mild COPD may benefit from PR; however, insufficient evidence is still available. Studies with robust designs and with longer follow-up times should be conducted.

# Introduction

COPD, independent of its severity, impacts the lives of patients and families as well as on health-care systems (Hilleman, Dewan, Malesker, & Friedman, 2000; Miravitlles, Murio, Guerrero, & Gisbert, 2003). Therefore, it is imperative to plan health care for patients with COPD at all grades.

rehabilitation is defined Pulmonary as "an evidence-based, multidisciplinary, and comprehensive intervention for patients with chronic respiratory diseases who are symptomatic and often have decreased daily life activities" (Nici et al., 2006). This intervention is a recommended standard of care in the management of patients with COPD and typically combines exercise training, education and psychosocial support (Martín-Valero, Cuesta-Vargas, & Labajos-Manzanares, 2012; Nici et al., 2006). A meta-analysis conducted by Lacasse et al suggests that pulmonary rehabilitation is effective in relieving dyspnea and fatigue and in improving patients' health-related quality of life (HRQOL) (Lacasse, Goldstein, Lasserson, & Martin, 2006). However, in this meta-analysis only studies including patients with moderate, severe, and very severe COPD were analyzed.

Recent evidence showed that physical activity levels, quadriceps strength, and HRQOL can be already impaired in patients with mild COPD (best recorded FEV<sub>1</sub>  $\ge$  80% of the predicted)(Maltais, Dennis, & Chan, 2013; Shrikrishna et al., 2012; Vestbo et al., 2013), and these impairments worsen over time (Maltais et al., 2013). Therefore, patients at this grade may also benefit from pulmonary rehabilitation programs. A systematic review about the influence of physical activity on mild-to-moderate COPD showed that physical activity significantly improved patients' physical fitness; however, no statistically significant beneficial effects were seen on HRQOL or dyspnea (Chavannes, Vollenberg, van Schayck, & Wouters, 2002). Furthermore, the great proportion of patients analyzed in this review had moderate COPD. Therefore, the impact of pulmonary rehabilitation programs on patients with mild COPD remains unestablished. Thus, this systematic review aimed to assess the impact of pulmonary rehabilitation on exercise capacity, HRQOL, health-care resource use, and lung function in patients with mild COPD.

# Methods

# Search strategy

A systematic literature search was conducted between January and April 2013 on the following databases: Web of knowledge (1970-2013), EBSCO (1974-2013), MEDLINE (1948-2013), and SCOPUS (1960-2013). The search terms used were organized using the PICO (Population, Intervention, Comparison, and Outcome) framework (Schardt, Adams, Owens, Keitz, & Fontelo, 2007), the definition of Comparison (C) was omitted as it was aimed at finding a range of study designs, as follows: "COPD" OR "chronic obstructive pulmonary disease" OR "chronic bronchitis" OR emphysema OR "mild COPD" OR "early COPD" OR "GOLD 1" OR "GOLD I" AND "pulmonary rehabilitation" OR "respiratory rehabilitation" OR "exercise training" OR "physical activity" OR exercise AND "exercise capacity" OR "health-related quality of life" OR "health-care resource" use" OR "lung function" OR "FEV1". The reference lists of the included studies were hand searched for other potentially eligible studies. This systematic review was reported according to the PRISMA Group statement for preferred reporting items for systematic reviews and meta-analyses (Moher, Liberati, Tetzlaff, Altman, & on behalf of the PRISMA group, 2009).

# Selection criteria

According to the PICO framework, studies were included if they met the following inclusion criteria.

Patients with mild COPD (FEV<sub>1</sub> ≥80% of the predicted (Vestbo et al., 2013))

2. Pulmonary rehabilitation program (inpatient, outpatient or home-based care) of at least 4 weeks (Lacasse et al., 2006; Martín-Valero et al., 2012) that

included exercise training with or without any form of education and/or psychological support

3. Comparison: Standard medical treatment or none

4. Outcomes: at least one of the following: exercise capacity, HRQOL, health-care resource use, and lung function.

Studies were excluded if they did not include patients with mild COPD (studies with a subgroup of patients were retained in the analysis) and if they were review articles, abstracts of communications or meetings, conference proceedings papers, case reports, editorials, commentary to articles, study protocols, or unpublished papers. Papers without abstracts or written in languages other than English, Portuguese, and Spanish were also excluded.

#### Screening of studies

The authors independently reviewed the titles, abstracts, and key words of every record. If the information given in the title, abstract and/or key words suggested that the study might fit the inclusion criteria of the systematic review, the full article was retrieved for further assessment. From the full articles, the decision to exclude a study was based on the agreement of both authors. Disagreements were solved by reaching a consensus. Studies that did not fulfill the selection criteria of the systematic review were excluded. Once a study was excluded, a record of the article, including the reason for exclusion, was retained.

# Quality assessment

The methodological quality of each included study was independently assessed by the two authors, based on the checklist created by Downs and Black (Downs & Black, 1998). This checklist assesses the quality of both randomized and non-randomized studies of health-care interventions, and it is composed of 27 questions split into 5 sections: reporting; external validity; internal validity – bias; internal validity – confounding, and power (Downs & Black, 1998). According to previous systematic reviews (Chudyk, Jutai, Petrella, & Speechley, 2009; Samoocha, Bruinvels, Elbers, Anema, & van der Beek, 2010), the scoring

for question 27 dealing with statistical power was simplified to a choice of awarding either 1 point or 0 points, depending on whether there was sufficient power to detect a clinically important effect. The scores of the Downs and Black checklist can be grouped into four quality levels: ≤14, poor; 15-19, fair; 20-25, good; and 26-28, excellent (Chudyk et al., 2009; Samoocha et al., 2010).

#### Data extraction

The authors independently extracted data from the included studies. Disagreements were discussed until consensus was reached. Data from the articles were extracted in a structured table format, according to the topics: first author's last name and year of publication, study design, participants' characteristics, type of intervention(s) or comparator(s) (if there were any), outcome measures used, and quantitative findings.

# Data analysis

To determine the consistency of the quality assessment performed by the 2 authors, an inter-observer agreement analysis using Cohen's kappa was performed. The value of Cohen's kappa ranges from 0 to 1, and can be categorized as slight (0.0-0.20), fair (0.21-0.40), moderate (0.41-0.60), substantial (0.61-0.80), or almost perfect (≥0.81) agreement (Landis & Koch, 1977). This statistical analysis was performed using PASW Statistics (version 18.0, SPSS Inc., Chicago, Illinois).

Because of the different designs and outcome measures used in the selected studies a meta-analysis was not possible to conduct. To analyze the effects of pulmonary rehabilitation on mild COPD, the effect sizes were computed for the outcomes of interest. The effect sizes were interpreted as low (0.20), medium (0.50), and high (0.80) effect magnitudes (Cohen, 1988). All quantitative data analyzes were performed using the software Comprehensive Meta-Analysis version 2 (Biostat, Englewood, New Jersey) (Borenstein, Hedges, Higgins, & Rothstein, 2005).

# Results

#### Study selection

The databases search identified 5,728 records. After the removal of duplicates, 4,766 records were screened for relevant content. During the title, abstract, and key word screening, 4,745 articles were excluded. The full text of 21 potentially relevant articles was assessed, and 11 articles were excluded for the following reasons: (1) patients with mild COPD were not include (n=8); (2) the effect of pulmonary rehabilitation programs was not assessed with the outcome measures of interest (n=1); (3) quantitative data were not provided (n=1); and (4) the study was not written in English, Portuguese, or Spanish (n=1). Ten studies were retained. Eight of these studies included patients with mild COPD; however, results were not presented by COPD grade. The corresponding authors were contacted to provide data on patients with mild COPD. Only Liu et al (Liu et al., 2012) made available the requested data, and therefore their study was included. The other 7 studies were excluded. Therefore, 3 original articles were included. The search for relevant articles within the reference list of the selected articles did not retrieve any further study (Fig. 1).



Figure 1. Flowchart of included studies

# Quality assessment

The articles included in this review scored 14-20 on the Downs and Black scale (Downs & Black, 1998) with a mean of  $16.7 \pm 3.1$  (Table 1). The agreement between the 2 authors was substantial (kappa=0.686; 95% CI 0.507-0.842; p=.001). Results indicate that the quality of the studies varied among poor (Golmohammadi, Jacobs, & Sin, 2004), fair (Riario-Sforza et al., 2009), and good (Liu et al., 2012). The 3 studies scored particularly poorly in the following items: description of adverse events, sample representativeness, patient and assessor blinding, adjustment for confounding factors in the analysis, and power.

# Study characteristics

Study characteristics are presented in Table 2. The included studies had different designs that included retrospective (Golmohammadi et al., 2004), one group pretest-posttest (Riario-Sforza et al., 2009), and randomized controlled (Liu et al., 2012). The 3 studies recruited a total of 100 patients receiving specialized care. Golmohammadi et al (Golmohammadi et al., 2004) did not provide data on age and gender ratio of the 31 patients with mild COPD included. In the other 2 studies, age ranged from 41 to 83 y, and the number of male patients included were approximately double the number of female patients (47:22).

The pulmonary rehabilitation programs implemented by Golmohammadi et al (Golmohammadi et al., 2004) and by Riario-Sforza et al (Riario-Sforza et al., 2009) were both out-patient programs, with duration between 6 and 8 weeks, and frequency between 2 and 3 sessions a week. The exercise training sessions lasted between 60 and 90 min, and included mainly aerobic training, strength training, and respiratory muscle training. Both programs included an educational component. Liu et al (Liu et al., 2012) implemented a home-based pulmonary rehabilitation program, consisting of 1 week of pursed-lip breathing and aerobic training under the supervision of health professionals followed by 6 months of peer-led walking and participation in ball games for 60 minutes twice a week. This study also had a control group that received standard medical treatment, consisting of health education and recommendations to exercise by themselves.

																Inter	mal Va	alidity										
Studies	Reporting							External Validity			Bias					Confounding					Power	Total						
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	
Golmohamma-	1	1	1	1	0	1	1	0	1	1	0	0	1	0	0	1	0	1	1	1	0	0	0	0	0	1	0	14
di et al (2004)																												
Riario-Sforza	1	1	1	1	1	1	1	0	0	1	0	0	1	0	0	1	1	1	1	1	1	1	0	0	0	0	0	16
et al (2009)																												
Liu et al (2012)	1	1	1	1	1	1	1	0	1	1	0	0	0	0	1	1	1	1	1	1	1	1	1	1	0	1	0	20

Table 1. Quality assessment using the Downs and Black Scale (1998)

Studies	Design Participants		Intervention	Outcome Measures	Findings
Golmohammadi	Retrospective	31 patients with	Setting: out-patient	SGRQ symptoms	SGRQ symptoms: Pre 48.3; Post 42.3; p=.07
et al (2004)		mild COPD	Duration: 6 or 8 wk	SGRQ activity	SGRQ activity: Pre 55.3; Post 48.7; p=.01
			Frequency: 2 or 3 times/wk	SGRQ impact	SGRQ impact: Pre 30.8; Post 23; p=.01
			Exercise training	Emergency	Emergency department visits: Pre 41.2 ± 13; Post 13.6 ± 7.9; p=.085
			Duration: 90 min	department visits	Hospitalization days: Pre 123.9 ± 75; Post 12.9 ± 12.9; p=.043
			Components: breathing exercises,	Hospitalization days	
			endurance training, upper extremity		
			strength training, inspiratory muscle		
			training		
			Education: adaptations in activities of		
			daily living, relaxation techniques,		
			nutritional counseling, psychosocial		
Diaria Charge at	0	07 notionto with	support.		
Riario-Storza et	One group	37 patients with		6IVIVVD	6MWD: Pre 355 $\pm$ 63m; Post 418 $\pm$ 78m
al (2009)	Pretest-		Duration: 6 wk		
	posttest	24M,13F	Frequency: 2 times/wk		
		64.6 ± 9.8	Exercise training		
		(41-83) y	Duration: 90 min		
			Components: warm-up, endurance		
			training, strength training of the arm,		
			shoulder and trunk muscle groups;		
			respiratory muscle training.		
			Education		

Table 2. Impact of pulmonary rehabilitation programs in patients with mild COPD

Liu et al (2012)	RCT	Experimental	Experimental group	6MWD	Experimental group				
		group	Setting: Home-based	Zhongshan COPD	6MWD: Pre 407.4 ± 16.9m; Post 444.6 ± 22.5m; p=.001				
		15 patients with	Duration: 6 mo	questionnaire:	Zhongshan COPD questionnaire				
		mild COPD	Frequency: 2 times/wk	- ADL	ADL: Pre 22 ± 3.1; Post 19.5 ± 2.7; p=.001 Anxiety: Pre 13.9 ± 2.4; Post 12.3 ± 1.7; p=.002				
		10M, 5F	Exercise training	- Anxiety					
		56.4 ± 8.2	Duration: 60 min	- Depression	Depression: Pre 12.3 ± 1.7; Post 11.1 ± 1.4; p=.011				
		(46-72) y	Components: walking and	- Social participation	Social participation: Pre 12.7 $\pm$ 2.5; Post 12.7 $\pm$ 1.9; p=.892				
		Control group 17 patients with	participation in ball games	- Total score	Total Score: Pre 60.8 ± 5.4; Post 55.7 ± 4.8; p=.001				
			Education: pursed-lip breathing,	Hospitalizations due	Hospitalizations: Pre 1.2 $\pm$ 0.4; Post 1 $\pm$ 0.4; p=.082				
			aerobic exercises.	to AECOPD	FEV <sub>1</sub> : Pre 87.2 ± 4.1% predicted; Post 87.5 ± 3.7% predicted; p=.442				
		13M, 4F 58.9 ± 6 (46-67) y	Control group Standard medical treatment: health education, advised to continue exercising.	FEV <sub>1</sub>	Control group 6MWD: Pre 403.1 ± 21m; Post 401.6 ± 26.7m; p=.756 Zhongshan COPD questionnaire ADL: Pre 21.3 ± 3.2; Post 20.8 ± 2.8; p=.324 Anxiety: Pre 14 ± 2.9; Post 14.35 ± 2.9; p=.496 Depression: Pre 12.1 ± 2.0; Post 11.9 ± 2; p=.699 Social participation: Pre 12.7 ± 2.5; Post 12.2 ± 2.3; p=.245				
					Total score: Pre 60.1 ± 4; Post 59.2 ± 3.3; p=.440				
					Hospitalizations: Pre 1.3 $\pm$ 0.6; Post 1.1 $\pm$ 0.5; p=.083				
					FEV <sub>1</sub> : Pre 87.7 ± 5%predicted; Post 86.7 ± 4.3%predicted; p=.221				

Data are presented as mean± SD. SGRQ= St George Respiratory Questionnaire M= male F= female RCT= randomized controlled trial 6MWD= 6-min walk distance ADL= activities of daily living AECOPD= acute exacerbation of COPD Pre= pretest Post= posttest

# Synthesis of the results

Exercise capacity

Exercise capacity was assessed in 2 studies by the 6-min walk distance (Liu et al., 2012; Riario-Sforza et al., 2009). Significant improvements in exercise capacity were found when comparing pretest-posttest data (effect size [ES] 0.87 (Riario-Sforza et al., 2009)) and when comparing PR with standard medical treatment (ES 1.82 (Liu et al., 2012)).

# HRQOL

HRQOL was measured in 2 studies using distinct instruments, that is, the St George Respiratory Questionnaire (SGRQ) (Golmohammadi et al., 2004) and the Zhongshan COPD questionnaire (Liu et al., 2012). A small improvement in SGRQ symptoms (ES 0.34) and activity (ES 0.49) scores, and a medium improvement in SGRQ impact score (ES 0.66) were found after pulmonary rehabilitation (Golmohammadi et al., 2004). A significant improvement in HRQOL (Zhongshan COPD questionnaire total score) favored the pulmonary rehabilitation group (ES 0.86) (Liu et al., 2012). The Zhongshan COPD questionnaire also provided information on 4 subscales of HRQOL: activity of daily living, social participation, depression, and anxiety. Improvements in anxiety (ES 0.85), activity of daily living (ES 0.47), and in depression (ES 0.46) favored the pulmonary rehabilitation group. Social participation did not change significantly in any of the groups (ES 0.24).

# Health Care resource use

The number of hospitalization days were decreased after pulmonary rehabilitation (ES 0.38) (Golmohammadi et al., 2004). The number of emergency department visits also decreased (ES 0.32) (Golmohammadi et al., 2004). The number of hospitalizations in the pulmonary rehabilitation group after 6 months was not significantly different from that of the control group (ES 0.22) (Liu et al., 2012).

Lung function

Pulmonary rehabilitation had no significant effect in lung function (ES 0.2) (Liu et al., 2012).

#### Discussion

Most of the pulmonary rehabilitation programs implemented in the 3 studies analyzed had significant positive effects on the exercise capacity and HRQOL of patients with mild COPD. However, the effects of these programs on health-care resource use and lung function were inconclusive.

Two studies analyzed the impact of pulmonary rehabilitation on exercise capacity with the 6-min walk test, and a statistically significant improvement was found (Liu et al., 2012; Riario-Sforza et al., 2009). The improvement in the distance walked after pulmonary rehabilitation was ~37 m in one study (Liu et al., 2012) and 63 m in the other (Riario-Sforza et al., 2009). Since the minimally important difference for the 6-min walk test is expected to be between 25 and 35 m in patients with moderate and severe COPD (Holland et al., 2010; Puhan et al., 2008), we can hypothesize that in both studies the clinically important effect was achieved. Nevertheless, this has to be interpreted with caution, as the minimally important difference for the 6-min walk distance in patients with mild COPD has not been established.

The HRQOL was assessed using two instruments: the SGRQ (Golmohammadi et al., 2004) and the Zhongshan COPD questionnaire (Cai, Li, & Fang, 2004). In the study of Golmohammadi et al (Golmohammadi et al., 2004), the improvements were all statistically significant, with the exception of the SGRQ symptoms domain. Lacasse et al and Puhan et al, reviewing the benefits of pulmonary rehabilitation in patients with COPD, also verified that the results of the SGRQ symptoms domain were not statistically significant (Lacasse et al., 2006; Puhan et al., 2011). These findings suggest that this SGRQ domain may be the less responsive to pulmonary rehabilitation programs. In the study of Liu et al., 2012) statistically significant improvements in HRQOL favored

pulmonary rehabilitation in comparison with the standard medical treatment. The pulmonary rehabilitation programs implemented in the studies by Liu et al (Liu et al., 2012) and Golmohammadi et al (Golmohammadi et al., 2004) improved the HRQOL of patients with mild COPD. Because physical activity levels and HRQOL can be impaired in patients with mild COPD (Maltais et al., 2013; Shrikrishna et al., 2012), and the limited evidence available shows that these health domains can be improved with pulmonary rehabilitation programs, more studies with robust study designs are needed to establish these benefits at an early stage of the disease.

Prevention of respiratory exacerbations is one of the major goals of COPD management (Puhan et al., 2011). The effects of pulmonary rehabilitation on the number of exacerbations was not directly assessed in any of the included studies, instead health-care resource use was examined. Pulmonary rehabilitation did not have a statistically significant effect on the number of hospitalizations when compared with standard medical treatment (Liu et al., 2012). A statistically significant decrease in the number of emergency department visits after pulmonary rehabilitation was also not found; however, a significant decrease in the number of hospitalization in preventing exacerbations and its severity remains unclear. This is mainly due to the lack of studies, but probably is also due to the implementation of pulmonary rehabilitation programs with distinct training regimens and therefore different effects of dosage (Martín-Valero, Cuesta-Vargas, & Labajos-Manzanares, 2010).

Pulmonary rehabilitation had no effect on lung function (Liu et al., 2012). This was expected because previous studies have shown that no changes in lung function were observed in patients with moderate-to-very-severe COPD after conventional pulmonary rehabilitation programs (Niederman et al., 1991; Zwick et al., 2009). However, a matched controlled trial performed in patients with moderate and severe COPD shows that after 3 y of out-patient pulmonary rehabilitation the decline in FEV<sub>1</sub> was significantly lower in the pulmonary

rehabilitation group compared with the control group (standard treatment) (Stav, Raz, & Shpirer, 2009). In patients with mild COPD, it is still unknown whether in the long run pulmonary rehabilitation can delay the decline of lung function and therefore disease progression. This needs to be investigated in well-designed longitudinal studies.

This review has important limitations that need to be considered. First, only 3 studies with small sample sizes were included, and the oldest was published in 2004. This may be because of the difficulty in recruiting patients with mild COPD, because most of them are asymptomatic and do not look for medical assistance. Additionally, this may be a result of the relatively new interest of pulmonary rehabilitation research in mild COPD and of publication bias (studies with statistically significant results are more likely to be published than those with nonsignificant results). Second, a number of well-designed studies including patients with mild COPD were excluded as results were not individualized by COPD grade. The inclusion of these studies would probably consolidate the findings of this review. Third, all studies had different methodological designs and implemented different pulmonary rehabilitation programs regarding the setting, duration, and components. This might be due to the absence of specific quidelines for pulmonary rehabilitation programs for patients with mild COPD. Further research from randomized controlled trials is therefore needed to define the most appropriate specificities of pulmonary rehabilitation for this population. Fourth, mainly the short-term effects of pulmonary rehabilitation were assessed. Only Golmohammadi et al. (Golmohammadi et al., 2004) analyzed the benefits of pulmonary rehabilitation in terms of emergency department visits and hospitalization days 1 y after pulmonary rehabilitation. However, the long-term benefits of pulmonary rehabilitation in terms of exercise capacity and HRQOL for patients with mild COPD remains uncertain. Therefore, long-term studies are also required.

# Conclusions

Most of the pulmonary rehabilitation programs implemented in the included studies had significant positive effects on the exercise capacity and HRQOL of patients with mild COPD. Nevertheless, the effects of these programs on healthcare resource use and lung function were inconclusive. This systematic review suggests that patients with mild COPD may benefit from pulmonary rehabilitation as part of the management of their disease; however, insufficient evidence is still available. Further research with robust study designs and longer follow-up times is urgently needed to inform guidelines for pulmonary rehabilitation in patients with mild COPD.

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Systematic Review II

# Computerized respiratory sounds in patients with COPD: a systematic review

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## Abstract

Computerized respiratory sound analysis provides objective information about the respiratory system and may be useful to monitor patients with chronic obstructive pulmonary disease (COPD) and detect exacerbations early. For these purposes, a thorough understanding of the typical computerized respiratory sounds in patients with COPD during stable periods is essential. This review aimed to systematize the existing evidence on computerized respiratory sounds in stable COPD. A literature search in the Medline, EBSCO, Web of Knowledge and Scopus databases was performed. Seven original articles were included. The maximum frequencies of normal inspiratory sounds at the posterior chest were between 113 and 130 Hz, lower than the frequency found at trachea (228 Hz). During inspiration, the frequency of normal respiratory sounds was found to be higher than expiration (130 vs. 100 Hz). Crackles were predominantly inspiratory (2.9-5 vs. expiratory 0.73-2) and characterized by long durations of the variables initial deflection width (1.88-2.1 ms) and two cycle duration (7.7-11.6 ms). Expiratory wheeze rate was higher than inspiratory rate. In patients with COPD normal respiratory sounds seem to follow the pattern observed in healthy people and adventitious respiratory sounds are mainly characterized by inspiratory and coarse crackles and expiratory wheezes. Further research with larger samples and following the Computerized Respiratory Sound Analysis (CORSA) guidelines are needed.

## Introduction

Chronic Obstructive Pulmonary Disease (COPD) is an important cause of morbidity and mortality worldwide (Mannino & Braman, 2007), projected to be the seventh leading cause of years lived with disability by 2030 (Mathers & Loncar, 2006). The COPD trajectory is usually marked by frequent acute exacerbations (Vestbo et al., 2013), that lead to patients' health status deterioration and account for the greatest proportion of the COPD burden on the health care systems (Anzueto, 2010; Seemungal, Hurst, & Wedzicha, 2009). Therefore, significant research efforts have been dedicated to improve the prevention and early detection of exacerbations.

Auscultation of respiratory sounds is widely used by health professionals for monitoring respiratory diseases (Marques, Bruton, & Barney, 2006), such as COPD, as it provides information about the respiratory function and structure that cannot be obtained with any other simple and non-invasive method (Forgacs, 1978). However, auscultation with a stethoscope is a subjective process depending on human's ear auditory system and memory capacities (Welsby, Parry, & Smith, 2003), terminology used, qualitative nature of respiratory sounds (Polat & Guler, 2004) and stethoscope acoustics specifications (Welsby & Earis, 2001).

Computerized respiratory sound analysis, which consists of recording patients' respiratory sounds with an electronic device and classifying/analyzing them based on specific signal characteristics, overcomes the identified limitations with the standard auscultation (Kandaswamy, Kumar, Ramanathan, Jayaraman, & Malmurugan, 2004; Moussavi, Leopando, Pasterkamp, & Rempel, 2000; Polat & Guler, 2004). Nevertheless, the implementation of computerized respiratory sound analysis alone is insufficient to improve the diagnostic value of auscultation in monitoring patients with COPD and in detecting COPD exacerbations. Even with an objective method, health professionals cannot interpret with confidence the computerized respiratory sound analysis findings (e.g., presence/absence of an exacerbation), without a clear definition of what are the typical auscultation

findings in patients with COPD during stable periods. Thus, this review aimed to systematize the existing evidence on computerized respiratory sounds in stable COPD.

## Methods

## Search strategy

An extensive literature search was performed from March to May 2013 in the following electronic databases Medline (1948-2013), EBSCO (1974-2013), Web of Knowledge (1970-2013) and Scopus (1960-2013) databases. The search terms were based on a combination of the following keywords: (COPD OR "chronic obstructive pulmonary disease" OR "chronic bronchitis" OR emphysema) and ("auscultation" OR "digital auscultation" OR "electronic auscultation" OR "computerized analyses" OR "digital signal process\*" OR "acoustic signal process\*" OR "computerized lung sound analysis" OR "automated classification of lung sounds") and ("lung sounds" OR "breath sounds" OR "respiratory sounds" OR "Adventitious lung sounds" OR "Adventitious sounds" OR Crackle\* OR Wheez\*). The search terms were limited to titles and abstracts. The reference lists of the selected articles were scanned for other potential eligible studies. This systematic review was reported according to preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines (Moher, Liberati, Tetzlaff, Altman, & on behalf of the PRISMA group, 2009).

## Eligibility criteria

According to the PICO (Population, Intervention, Comparison, and Outcome) framework, studies were included if they met the following inclusion criteria:

- i) Population: patients with COPD;
- ii) Intervention: none;
- iii) Comparison: none;

iv) Outcomes: parameters of computerized respiratory sounds (normal and/or adventitious respiratory sounds).

Articles were also included if i) were full papers published as original articles or in conference proceedings and ii) were written in English, Portuguese, Spanish or French. Articles were excluded when the respiratory sounds were characterized through standard auscultation. Book chapters, review papers, abstracts of communications or meetings, letters to the editor, commentaries to articles, unpublished work and study protocols were also excluded from this review.

# Study selection

Duplicates were first removed. Then, the title, abstract and keywords were analyzed to assess the type and relevance of the publication for the scope of the review. If the publication was potentially relevant for the scope of the review, the full-text was screened for content to decide their inclusion. The two reviewers decided the articles inclusion and disagreements were solved by consensus.

#### Data extraction

Data from the included articles were extracted in a structured table-format, i.e.: first author's last name and year of publication, study design, participants, data collection protocol, data analyses, outcomes and quantitative findings.

## Quality assessment

The quality of the included studies was assessed with the 'Crombie criteria' for assessment of cross-sectional studies (Crombie, 1996; Petticrew & Roberts, 2006). The 'Crombie criteria' assesses mainly the research design, the sample recruitment and representativeness, the reliability of the measurements and the statistical analysis. The quality of each study was assessed independently by the two reviewers and when disagreements occurred, consensus was achieved through discussion.

## Data analysis

To determine the consistency of the quality assessment performed by the two reviewers, an inter-observer agreement analysis using the Cohen's kappa was performed. The value of Cohen's kappa ranges from 0 to 1 and can be categorized as slight (0.0-0.20), fair (0.21-0.40), moderate (0.41-0.60), substantial (0.61-0.80) or almost perfect (≥0.81) agreement (Landis & Koch, 1977). This statistical analysis was performed using IBM SPSS Statistics version 20.0 (IBM Corporation, Armonk, NY, USA).

## Results

## Study selection

The database search identified 68 records. After duplicates removal, 60 records were screened for relevant content. During the title, abstract and keyword screening, 46 articles were excluded. The full-text of the 14 potentially relevant articles was assessed and 8 articles were excluded due to the following reasons: use of standard auscultation to characterize respiratory sounds (n=4), detection of adventitious respiratory sounds through imaging techniques (n=3) and results from patients with COPD were not individualized (n=1). Six original articles were selected. The search for relevant articles within the reference list of the selected articles retrieved 1 study which was also included. Therefore, 7 original articles were included in this review (see Figure 1).



Figure 1. PRISMA flow diagram of the included studies

#### Quality assessment

The quality of the included studies, using the 'Crombie criteria', is presented in Table 1. All studies included had an appropriate research design and used objective measures. Two studies failed in reporting the recruitment strategy used (Murphy, 2008; Piirila, Sovijarvi, Kaisla, Rajala, & Katila, 1991). As no study reported dropouts, the response rate indicator was considered in all

Table 1. Quality assessment based on the 'Crombie criteria'

	Appropriate	Appropriate	Response	Sample	Objective and	Power	Appropriate	Evidence of	Quality
	Research	Recruitment	Rate	Representa-	Reliable	Calculation/	Statistical	Bias	Indicators Met
	Design	Strategy		tiveness	Measures	Justification of	Analysis		
Author						Numbers			
(year)									
Piirila et al. (1991)	*		•		<b>♦</b>		*		4/8
Munakata et al. (1991)	*	•	•		•		•		5/8
Bettencourt et al. (1994)	*	•	•		•		•		5/8
Malmberg et al. (1995)	•	•	•		•		*		5/8
Fiz et al. (2002)	•	•	•		•		•		5/8
Taplidou et al. (2007)	•	•	•		•		•		5/8
Murphy (2008)	•		•		•		*		4/8

studies. All presented the statistical analyses used, with one exception (Murphy, 2008), which were appropriate. Studies did not use representative samples or justified their size. Evidence of bias was not considered present, despite the use of convenience samples. The agreement between the two reviewers was substantial (k=0.714; 95% CI 0.532-0.892; p=0.001).

## Study characteristics

A total of 164 patients with stable COPD participated in the included studies. All studies, with one exception (Murphy, 2008), provided data regarding patients' mean age, which ranged from 46 to 66.3 years old. Patients' mean forced expiratory volume in 1 second (FEV<sub>1</sub>) ranged between 36 and 54.5% of the predicted (Fiz et al., 2002; Malmberg, Pesu, & Sovijarvi, 1995; Piirila et al., 1991; Taplidou & Hadjileontiadis, 2007).

The protocols used to record the respiratory sounds were different in all studies. Piirila et al. (1991) (Piirila et al., 1991) reported that respiratory recordings were obtained with the patient in the sitting position. The other authors were not clear about the patients' body position during the recordings. Respiratory sounds were recorded while patients breathed with an airflow between 1 and 1.5 L/s (Malmberg et al., 1995; Piirila et al., 1991; Taplidou & Hadjileontiadis, 2007) and during forced expiratory maneuvers (Fiz et al., 2002). However, some studies did not report the respiratory maneuvers used during the respiratory sounds recordings (Bettencourt, Delbono, Spiegelman, Hertzmark, & Murphy, 1994; Munakata et al., 1991; Murphy, 2008).

Respiratory sounds were recorded with microphones (condenser (Malmberg et al., 1995), electret condenser (Bettencourt et al., 1994; Munakata et al., 1991; Taplidou & Hadjileontiadis, 2007) and miniature electret (Murphy, 2008)) and piezoelectric contact sensors (Fiz et al., 2002; Malmberg et al., 1995). Two studies recorded respiratory sounds only at one chest location: at trachea (Fiz et al., 2002) and at the base of the right posterior chest (Munakata et al., 1991). However, the majority of studies recorded respiratory sounds in more than one chest location: i) at chest sites with abnormal sounds (Bettencourt et al.,

1994); ii) at trachea and at the base of the right posterior chest (Malmberg et al., 1995); iii) at posterior right/left chest (Piirila et al., 1991); iv) at trachea, right/left axillae and right/left posterior bases (Taplidou & Hadjileontiadis, 2007); and trachea, lateral bases and posterior chest (Murphy, 2008).

Regarding pre-processing methods, five studies reported the methods used to filter the respiratory sounds signals. In two studies, high- and low-pass filters were used, with cut-off frequencies from 50–100 Hz and from 4,000-5,000 Hz (Malmberg et al., 1995; Piirila et al., 1991). Three studies, instead, used band-pass filters (80-2,000 Hz (Bettencourt et al., 1994; Fiz et al., 2002) and 60–2,100 Hz (Taplidou & Hadjileontiadis, 2007)). In relation to digitization protocols, five studies described the sampling rates used, which ranged from 5,000 Hz to 20,000 Hz (Fiz et al., 2002; Malmberg et al., 1995; Munakata et al., 1991; Piirila et al., 1991; Taplidou & Hadjileontiadis, 2007).

The characteristics of the respiratory sounds were mainly explored using frequency analyses (Fiz et al., 2002; Malmberg et al., 1995; Munakata et al., 1991; Piirila et al., 1991; Taplidou & Hadjileontiadis, 2007). Fast Fourier Transform (FFT) analysis was used in four studies, one study used FFT alone (Malmberg et al., 1995), two combined FFT with time-expanded waveform analysis (Munakata et al., 1991; Piirila et al., 1991) and one combined FFT with algorithms (Fiz et al., 2002). Time-expanded waveform analysis alone (Bettencourt et al., 1994), a time-frequency wheeze detector (Taplidou & Hadjileontiadis, 2007) and an algorithm that automatically analyzed acoustic energy versus time (Murphy, 2008) were also used.

## Synthesis of the results

The results were summarized in two categories: normal respiratory sounds and adventitious respiratory sounds. Detailed information about each study is provided in table 2.

Author	Design	Participants	Data collection protocol	Data Analyses	Respiratory sounds	Findings
(Year)					outcomes	
Author (Year) Piirila et al. (1991)	Design Cross- sectiona I	Participants 10 patients with COPD 8M:2F 63 ± 6 yrs FEV <sub>1</sub> 51 ± 23% predicted	Data collection protocol Respiratory sound recordings: - acoustically isolated chamber - patient in a sitting position - 2 microphones (response range 4- 20,000 Hz), at the right and left posterior chest wall - airflow of 1 L/s, recorded with a pneumotacograph	Data Analyses Pre-filtration with a passive third order high-pass filter (cut-off frequency of 50 Hz) Amplification and filtration with a sixth order low-pass filter (cut-off frequency of 5,000 Hz) High-pass filter (cut-off frequency of 95 Hz) Sampling rate of 11,885 Hz 5-6 successive inspiratory and expiratory phases analyzed FFT to analyze normal respiratory sounds TEW to detect crackles	Respiratory sounds outcomesNormalrespiratorysounds:Fmax per BPFu per BPCrackles:N per BPUD per BPDD per BPBeginning, period and end point of cracklingInspiratory IDWInspiratory 2CDInspiratory LDWInspiratory TDWInspiratory TDWInspiratory TDW	FindingsNormal respiratory sounds:InspirationFmax 130 ± 30 HzFu 360 ± 80 HzExpirationFmax 100 ± 20 HzFu 260 ± 30 HzOrackles:InspirationN 2.9 ± 1.5UD 10%DD 90%Beginning 33 ± 24% of totalinspirationPeriod 20 ± 10% of total inspirationEnd point 51 ± 16% of totalinspirationIDW 2.1 ± 0.3 ms
						$2CD 11.6 \pm 1.1 \text{ ms}$ LDW 2.69 ± 0.34 ms TDW 12.4 ± 0.9 ms
						1011 12.7 10.0 110

Table 2. Computerized respiratory sounds in patients with COPD

						Expiration		
						N 0.73 ± 1.14		
						UD 47%		
						DD 53%		
Munakata et al. (1991)	Cross- sectiona I	10 patients with COPD	Respiratory sound recordings: - 1 electret condenser microphone at the base of the right posterior chest	Sampling rate of 20,000 Hz 5 crackles from one inspiratory phase	Inspiratory crackles: IDW	Inspiratory crackles: IDW 1.88 $\pm$ 0.05 ms		
		40.0 ± 10.0 yis	wall	TEW to detect crackles	1/4CD 9/4CD	1/4CD 1.16 ± 0.03 ms 9/4CD 8.79 ± 0.38 ms		
				FFT with a Hanning window for crackles' frequency analysis	2CD	$2CD 7.74 \pm 0.32 \text{ ms}$		
				Extraction of the single waveform signal by cutting at two zero points, before and after the waveform, and inserted into a continuous zero baseline to eliminate background noises	Fpeak	Fpeak 233 ± 8 Hz		
Bettencourt	Cross-	20 patients with	Respiratory sound recordings:	2 breaths at 2-4 sites	Crackles:	Crackles:		
et al. (1994)	sectiona	COPD	- electret condenser microphone	Band-pass filter 80-2,000 Hz	IDW	IDW 0.91 ± 0.43 ms		
	I	9M:11F 62 ± 9 yrs	(connected to the diaphragm of a stethoscope chest piece) over chest sites with adventitious respiratory sounds	TEW to detect crackles	2CD	2CD 5.4 ± 2.4 ms		
					ZXS	ZXS 4.4 ± 2.1		
Malmberg	Cross-	17 patients with	Respiratory sound recordings:	Pre-filtration with a third order high-	Inspiratory normal	Inspiratory normal respiratory		
et al. (1995)	sectiona	COPD	- sitting position	pass filter (cut-off frequency of 50 Hz)	respiratory sounds:	sounds:		
	I	58(38-73) yrs	- 1 condenser microphone (free field	Amplifier with a flat (± 0-5 dB)	RMS	Chest		
			frequency response 3-20,000 Hz (-3 dB)) at the base of the right posterior	frequency response curve over 20- 20,000 Hz	Fmax	RMS 63.5 ± 4.4 dB		

		FEV <sub>1</sub> 36(16- 79)% predicted	chest wall, approximately 10 cm below the margin of the scapula and 15 cm to the right of the spine - 1 piezoelectric contact sensor (free field frequency response essentially	Sampling rate of 12,000 Hz Low-pass filter (cut-off frequency of 4,000 Hz) High-pass filter (cut-off frequency of 100 Hz)	F50 F75	Fmax 113 ± 17 Hz F50 201 ± 21 Hz F75 321 ± 51 Hz Trachea RMS 82 6 ± 3.1 dB
			flat (± 3 dB) within 100-1,500 Hz) at the trachea on the right side of the cricothyroid cartilage - airflow of 1-1.25 L/s, recorded with a pneumotacograph	FFT with a Hanning window to analyze normal respiratory sounds		Fmax 228 ± 340 Hz F50 753 ± 177 Hz F75 1239 ± 186 Hz
Fiz et al. (2002)	Quasi- experim ental	6 patients with COPD 6M:0F 58.8 ± 4.9 yrs FEV <sub>1</sub> 40.4 ± 11.9% predicted	Respiratory sound recordings: - 1 contact microphone (PPG sensor, flat response 50-1,800 Hz, resonance frequency of 2,600 Hz) at the trachea at the level of the cricoid cartilage - during forced expiratory maneuvers, after deep inspirations - airflow recorded with a pneumotachograph	Amplification and band-pass filter 80- 2,000 Hz Sampling rate of 5,000 Hz Mean of 3 forced expiratory maneuvers analyzed Modified version of the Shabtai-Musih et al.(Shabtai-Musih, Grotberg, & Gavriely, 1992) algorithm to detect airflow between 0.2-1.2 L/s and analyze sound signal segments of 128 points FFT with a Hanning window Wheeze-grouping algorithm to detect peaks located in a time-frequency space	Wheezes: N Monophonic W% Polyphonic W% Time without wheezes Fmean	Wheezes: N 10.4 ± 6.1 Monophonic W% 32.6 ± 19.0% Polyphonic W% 53.6 ± 25.5% Time without wheezes 13.7 ± 29.7% Fmean 669.4 ± 250.1 Hz

Taplidou	Cross-	7 patients with	Respiratory sound recordings:	Amplification and band-pass filter 60-	Wheezes:	Wheezes:
et al. (2007)	sectiona	COPD	- semi-quiet clinical laboratory	2,100 Hz	N per recording	N 42 ± 30.6
	I	presenting	- 5 electret condenser microphones	Sampling rate of 5,512 Hz		
		wheezes	(linear ±1.5 dB frequency response	Wheeze detector based on time-		
		4M:3F	of 65–5,000 Hz) at trachea, right and	frequency analysis		
		66.3 ± 12.0 yrs	left axillae and right and left bases of			
		FEV <sub>1</sub> 54.5 ±	the posterior chest wall			
		18.2% predicted	- airflow of 1.5 L/s, recorded with a			
			pneumotachograph			
			- 5 minutes of recording			
Murphy	Cross-	94 patients with	Respiratory sound recordings:	Algorithm analyses acoustic energy	Crackles:	Crackles:
(2008)	sectiona	COPD	- miniature electret microphones	versus time and detects wheezes,	N per BP	Inspiratory N 5 ± 6
	I		imbedded in a soft foam mat placed	rhonchi and crackles	Wheezes: W% per BP	Expiratory N 2 ± 3
			6 microphonos on the posterior			Wheezes:
			right base, 6 on the posterior left		Rhonchi:	Inspiratory W% 2 ± 8%
			base, 1 on the right lateral base, 1 on		R% per BP	Expiratory W% 12 ± 23%
			the left lateral base and 1 over the			Rhonchi:
			trachea			Inspiratory R% 3 ± 11%
						Expiratory R% 7 ± 19%

Data are presented as mean±standard deviation. BP: breathing phase; CD: cycle duration; COPD: Chronic Obstructive Pulmonary Disease; DD: Downward deflections; F: female; FEV1: forced expiratory volume in 1 second; F50: Upper frequency limits for the 2nd quartile; F75: Upper frequency limits for the 3rd quartile; FFT: Fast Fourier Transform analysis; Fmax: Maximum frequency; Fmean: Mean frequency; Fpeak: Peak frequency; Fu: Upper frequency at 20dB; IDW: initial deflection width; LDW: largest deflection width; M: male; N: number; R%: rhonch occupation rate; RMS: Total power spectra; TDW: total duration of the signal crackle; TEW: Time-expanded waveform analysis; UD: Upward deflections; W%: wheeze occupation rate; ZXS: Number of zero crossings in each crackle.

## Normal respiratory sounds

Two studies characterized normal respiratory sounds of patients with COPD, by breathing phase (Piirila et al., 1991) and only in the inspiratory phase (Malmberg et al., 1995). Similar maximum frequencies of normal inspiratory sounds acquired at the posterior chest wall, 130 Hz (Piirila et al., 1991) and 113 Hz (Malmberg et al., 1995), were reported. The total power spectra, maximum frequency, upper frequency limits for the 2nd and 3rd quartiles of the power spectra were higher in the respiratory sounds recorded at trachea than posterior chest (Malmberg et al., 1995). It was also showed that the maximum frequency and upper frequency at -20 dB were higher in inspiratory than expiratory respiratory sounds (Piirila et al., 1991).

## Adventitious respiratory sounds

Six of the included studies analyzed the characteristics of adventitious respiratory sounds: crackles (Bettencourt et al., 1994; Munakata et al., 1991; Murphy, 2008; Piirila et al., 1991), wheezes (Fiz et al., 2002; Murphy, 2008; Taplidou & Hadjileontiadis, 2007) and rhonchi (Murphy, 2008).

#### Crackles

The characteristics of inspiratory and expiratory crackles were explored by two studies (Murphy, 2008; Piirila et al., 1991). Munakata et al. (1991) only looked at inspiratory crackles and Bettencourt et al.(1994) did not differentiate between inspiratory and expiratory crackles. Inspiratory crackles (between 2.9 and 5) were more frequent than expiratory (between 0.73 and 2)(Murphy, 2008; Piirila et al., 1991). The variable initial deflection width (IDW) was found to be between 1.88 and 2.1 ms and the variable two cycle duration (2CD) between 7.74 and 11.6  $\pm$  1.1 ms (Munakata et al., 1991; Piirila et al., 1991). Shorter durations, IDW 0.91 ms and 2CD 5.4 ms, were however also reported (Bettencourt et al., 1994). The peak frequency of inspiratory crackles was found to be 233 Hz and the maximum frequency 394 Hz (Munakata et al., 1991). Piirila et al. also studied the direction of the crackles first deflection and verified that during inspiration the majority were

downward (90% vs. 10% upward) and during expiration were relatively similar (upward 47% vs. downward 53%) (Piirila et al., 1991).

#### Wheezes

The three studies that analyzed the characteristics of wheezes used different protocols to record the respiratory sounds and different recording devices. The number of wheezes identified during 5 minutes of normal breathing was on average 42 (Taplidou & Hadjileontiadis, 2007) and during forced expiratory maneuvers 10.4 (Fiz et al., 2002). During forced expiratory maneuvers, only 13.7% of the time was not occupied by wheezes, and most wheezes were polyphonic (53.6% vs. 32.6% monophonic) (Fiz et al., 2002). The mean frequency of the originated wheezes was 669.4 Hz (Fiz et al., 2002). Wheezes were found to be more frequent during expiration than in inspiration (12% vs. 2%) (Murphy, 2008).

#### Rhonchi

Expiratory rhonchi rate in patients with COPD was found to be higher than the inspiratory rate (7% vs. 3%) (Murphy, 2008).

## Discussion

The major findings of this systematic review were that i) normal respiratory sounds of patients with COPD follow the pattern observed in healthy people and ii) adventitious respiratory sounds are mainly characterized by inspiratory and coarse crackles and expiratory wheezes.

In patients with COPD, the maximum frequencies of normal inspiratory sounds at the posterior chest were between 113 (Malmberg et al., 1995) and 130 Hz (Piirila et al., 1991), recorded at 1 L/s (Piirila et al., 1991) and at 1-1.25 L/s (Malmberg et al., 1995). In a group of healthy people, Malmberg et al. (1995) found similar maximum frequencies (117 Hz) (Malmberg et al., 1995). Therefore, as pointed out by Scheur et al. (1992) and Malmberg et al. (1995), the frequency and intensity of normal respiratory sounds in patients with COPD are similar to

those found in healthy people (Malmberg et al., 1995; Schreur, Sterk, Vanderschoot, Vanklink, & Vanvollenhoven, 1992). The frequency of normal respiratory sounds was found to be higher during inspiration than expiration (Piirila et al., 1991). This finding is in line with previous literature describing the normal respiratory sounds of healthy people (Kompis, Pasterkamp, Oh, & Wodicka, 1997) and of people with chronic diseases, such as bronchiectasis, fibrosing alveolitis and asbestos-related pleural disease (Piirila et al., 2000; Piirila et al., 1991). Normal respiratory sounds at the trachea presented higher frequencies than sounds at the posterior chest. This difference has been explained by the specific characteristics of these chest locations. At trachea turbulent flows are generated, due to its large diameter and absence of a filter (Bohadana, 2000; Sovijärvi, Malmberg, et al., 2000). Conversely, at posterior chest the flow becomes laminar and the high frequencies are filtered by the parenchyma (Bohadana, 2000; Sovijärvi, Malmberg, et al., 2000).

In patients with COPD, crackles were more common during inspiration (between 2.9 and 5 (Murphy, 2008; Piirila et al., 1991)) than during expiration (between 0.73 and 2 (Murphy, 2008; Piirila et al., 1991)). These data is in accordance with the Computerized Respiratory Sound Analysis (CORSA) definition of crackles, "adventitious, discontinuous, explosive sound occurring usually during inspiration" (Sovijärvi, Dalmasso, et al., 2000). In healthy people, this crackling behavior is also verified, however, with fewer crackles identified in each breathing phase (inspiration  $1\pm 2$  vs. expiration  $1\pm 1$ ) (Murphy, 2008). In inspiratory crackles, the IDW was found to be between 1.88 and 2.1 ms (Munakata et al., 1991; Piirila et al., 1991) and the 2CD between 7.74 and 11.6 ± 1.1 ms (Munakata et al., 1991; Piirila et al., 1991). According to the CORSA, these time parameters are characteristic of coarse crackles, defined as "low pitched and with a high amplitude and long duration" (Sovijärvi, Dalmasso, et al., 2000). Bettencourt et al. (1994), in a group of patients with COPD, reported shorter durations of the IDW (0.91 ms) and of the 2CD (5.4 ms). However, as in this study the beginning of the crackle was manually annotated, these shorter durations may be explained by the known difficulty in determine the exact beginning of a crackle (Piirila & Sovijarvi, 1995). Another reason that could explain these results was the inclusion of patients with different disease severities, however, this is unknown as studies failed in characterizing patients' COPD grade and only Piirila et al. provided the values of the FEV<sub>1</sub>% predicted. In patients with idiopathic pulmonary fibrosis, bronchiectasis, pneumonia and fibrosing alveolitis shorter durations of IDW and 2CD have been found (Munakata et al., 1991; Piirila et al., 1991; Ponte, Moraes, Hizume, & Alencar, 2013).

Only three studies analyzed the characteristics of wheezes and all used different protocols to record the respiratory sounds (Fiz et al., 2002; Murphy, 2008; Taplidou & Hadjileontiadis, 2007), which limited the synthesis of the results. Only one study analyzed the presence of wheezes in patients with COPD during normal breathing and found an average of 42 wheezes recorded during 5 minutes (Taplidou & Hadjileontiadis, 2007). However, this study assessed a convenience sample of 7 patients, which already presented wheezes during standard auscultation, and therefore, this number of wheezes may not be typical in all patients with COPD. Murphy verified that wheezes were more frequent during expiration than in inspiration (12% vs. 2%) (Murphy, 2008). This is in line with the wheezes pattern found in healthy people, in patients with asthma, congestive heart failure and pneumonia (Murphy, 2008). During forced expiratory maneuvers, 86.3% of the time was occupied by wheezes, and the greatest part of wheezes generated were polyphonic (Fiz et al., 2002). Conversely, in patients with asthma, the majority of wheezes identified were monophonic and a lower wheeze rate was found (77.9%) (Fiz et al., 2002). This result was expected as wheezes are produced by fluttering of the airways and COPD is more associated with a reduction on bronchial stiffness than asthma (Meslier, Charbonneau, & Racineux, 1995).

Expiratory rhonchi rate in patients with COPD was higher than the inspiratory rate (7% vs. 3%) (Murphy, 2008). This was expected since this adventitious respiratory sound is a low-pitched wheeze (Sovijarvi, Vanderschoot,

& Earis, 2000). In healthy people, rhonchi are almost absent (average rate in inspiration  $0\pm1$  and expiration  $0\pm3$ ) (Murphy, 2008).

This systematic review has important limitations that need to be considered. The literature search was performed in four electronic databases (Medline, EBSCO, Web of Knowledge and Scopus). However, other electronic databases, such as the IEEE (Institute of Electrical and Electronics Engineers) Xplore, which is a resource for electrical engineering and computer science publications, were not used and thus other articles may have been missed. Nevertheless, as the search strategy was thorough and further complemented with the review of reference lists from the articles included, it is believed that this review contains the most relevant studies on the topic analyzed. The included studies met only 4/5 quality indicators from the 8 assessed in the Crombie criteria, indicating low/medium methodological quality. However, strict criteria for study methodological quality have only become common practice in recent years and most studies were published before 2000. Nonetheless, it is believed that the inclusion of these studies in this review provided valuable insights into respiratory sounds characteristics in COPD.

Only seven studies with small sample sizes were included demonstrating that the available evidence about computerized respiratory sounds in patients with COPD is still limited. Samples were mainly composed of young-old patients and with advanced disease. Therefore, the extent to which the conclusions of this review are also applicable to oldest-old patients with COPD or with early COPD remains unclear. Furthermore, in the studies analyzed, respiratory sounds characteristics have not been compared across different patients with COPD (e.g., age, gender, disease severity, smoking history, etc.), thus conclusions regarding the existence of different phenotypes on respiratory sounds could not be drawn. In a recent study with patients with acute exacerbations of COPD, it was possible to characterize the course of exacerbations into two phenotypes based on the variation of specific respiratory sound characteristics (Sánchez Morillo, Astorga Moreno, Fernández Granero, & León Jiménez, 2013). Future research should clarify if different phenotypes exist during stable phases or if they become evident only during exacerbation periods. FFT was used to analyze respiratory sounds in most studies. However, as respiratory sounds are non-stationary signals, conventional methods of frequency analysis may not be recommended (Sánchez Morillo et al., 2013). Instead, short-time fourier transform should be considered to characterize respiratory sounds in future studies (Sovijarvi et al., 2000).

A lack of standardization across all studies in the procedures used to record (patient' body position, respiratory maneuvers, chest locations, sensor type), analyze (filters, sampling rates, FFT, algorithms) and characterize (parameters selected) respiratory sounds was found. In a recent systematic review on respiratory sounds in healthy people, these methodological differences were also observed (Oliveira & Marques, 2014). Guidelines for research and clinical practice in the field of respiratory sounds have been published in 2000 by the CORSA project group (Sovijarvi et al., 2000). These guidelines standardized the instrumentation, ways of acquiring data, procedures and signal processing techniques as well as the respiratory sounds' nomenclature (Sovijarvi et al., 2000). Therefore, the inconsistence of the procedures was expected in studies conducted in the 90s, however, not in the three studies published after 2000. This lack of standardization made interpretation and synthesis of the results difficult. Future studies in the field of respiratory sounds should follow the CORSA guidelines.

The overall findings of this review, together with findings from future studies using advanced auscultation equipment and analysis methods, will establish the characteristics of respiratory sounds in patients with COPD. Since this relevant information can be obtained with a non-invasive and cost-effective method, the potential of computerized respiratory sounds to monitor patients' respiratory status, e.g., in telemedicine applications, has become evident.

# Conclusion

In patients with COPD normal respiratory sounds seem to follow the pattern observed in healthy people and adventitious respiratory sounds are mainly characterized by inspiratory and coarse crackles and expiratory wheezes. However, these conclusions were drawn based in few studies conducted with small sample sizes of patients with advanced COPD and presenting a high inconsistence among the procedures used. Further research with larger samples, incorporating patients with different age ranges and with all COPD grades, and following the CORSA guidelines are needed to define the characteristics of computerized respiratory sounds in patients with COPD.

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Chapter III

**Original studies** 

Study I

# Impact of pulmonary rehabilitation in patients with mild COPD

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# Abstract

**Background:** Pulmonary Rehabilitation (PR) is a core component of the management of patients with moderate-to-very-severe COPD. However, as impairments in quadriceps muscle strength and health-related quality of life (HRQOL) are already present in patients with mild COPD, there is a need to investigate whether PR could also be beneficial to these patients. Thus, this study assessed the impact of PR on patients with mild COPD.

**Methods:** A quasi-experimental study was conducted. Twenty-six participants ( $67.8 \pm 10.3$  years old; FEV<sub>1</sub>  $83.8 \pm 6.4\%$  of predicted) enrolled in a 12-week PR program with exercise training and psychoeducation. Lung function was assessed by spirometry, dyspnea with the Modified Medical Research Council questionnaire, functional balance with the Timed Up and Go test, muscle strength with 10-repetition maximum testing, exercise tolerance with the 6-m walk test, emotional state with the Depression, Anxiety and Stress Scales, and HRQOL with the St George Respiratory Questionnaire (SGRQ).

**Results:** Significant effects were observed on participants' dyspnea (p=.003; effect size [ES]=0.7), functional balance (p<.001; ES=0.8), shoulder flexor/knee extensor strength (p<.001; ES=1.2-1.3) and exercise tolerance (p<.001; ES=0.5). With the exception of the SGRQ impact score, the symptom (p<.001; ES=0.6), activity (p=.02; ES=0.4), and total (p=.005; ES=0.3) scores improved significantly after PR. The PR program had no significant effect on participants' lung function and emotional state.

**Conclusions:** Patients with mild COPD benefit from PR and could therefore be routinely included in these programs. Studies with more robust designs and with long-term follow-ups are needed to inform guidelines for PR in mild COPD.

## Introduction

Pulmonary rehabilitation (PR) is "a comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies which include, but are not limited to, exercise training, education, and behavior change, designed to improve the physical and psychological condition of people with chronic respiratory disease" (Spruit et al., 2013). A meta-analysis demonstrated that PR is effective in improving dyspnea and health-related quality of life (HRQOL) in patients with moderate-to-very-severe COPD (Lacasse, Goldstein, Lasserson, & Martin, 2006) and thus, it is currently recognized as a core component of the management of these patients (Martín-Valero, Cuesta-Vargas, & Labajos-Manzanares, 2010).

Recent evidence showed that quadriceps muscle strength and HRQOL are already impaired in patients with mild COPD (post-bronchodilator FEV<sub>1</sub>/FVC < 0.7 and an FEV<sub>1</sub> > 80% of the predicted (Shrikrishna et al., 2012; Vestbo et al., 2013). Therefore, as stated in the American Thoracic Society/European Respiratory Society statement on PR, there is a need to investigate the potential of PR in these patients (Spruit et al., 2013).

A preliminary study from Riario-Sforza et al found that, after a 6-week outpatient PR program, patients with mild COPD improved their exercise tolerance (Riario-Sforza et al., 2009). However, the effects of PR on other health domains have not yet been established. Thus, this study aimed to assess the impact of PR on the lung function, dyspnea, functional balance, muscle strength, exercise tolerance, emotional state and HRQOL of patients with mild COPD. In line with research conducted in more severe grades of COPD, it is hypothesized that patients with mild COPD will also benefit from PR and that these benefits will be observed in different health domains.

## Methods

Design and Participants

A quasi-experimental one group pretest-posttest design was used. Outpatients with mild COPD were recruited from 2 primary care centers. Inclusion criteria were diagnosis of mild COPD according to the Global initiative for chronic Obstructive Lung Disease (GOLD) criteria (post-bronchodilator FEV<sub>1</sub>/FVC < 0.7 and FEV<sub>1</sub> > 80% of predicted)(Vestbo et al., 2013), ≥18 years old, and clinical stability for 1 month prior to the study (i.e., no hospital admissions or exacerbations as defined by the GOLD (Vestbo et al., 2013)). Patients were excluded if they presented severe psychiatric, neurologic or musculoskeletal conditions (Nici & ZuWallack, 2010) and/or unstable cardiovascular disease that could interfere with their performance during the exercise training sessions. The study received full approval from the institutional ethics committee, and written informed consent was obtained before data collection.

## Intervention

A 12-week PR program with exercise training (3 sessions/week, 60 min each) and psychoeducation (1 session/week, 90 min) was conducted. The exercise training sessions were composed of:

1. A warm-up and a cool-down period including range-of-motion, stretching, low-intensity aerobic exercises and breathing techniques (5-10 min) (Martín-Valero, Cuesta-Vargas, & Labajos-Manzanares, 2012).

2. Endurance training (walking) at 60-80% of the average speed achieved during the 6-min walk test (6MWT; 20 min) (Jenkins, 2007). The training intensity was adjusted according to the patient's symptoms on the modified Borg scale (a rating of 4-6 on perceived dyspnea/fatigue was an indicator of adequate training intensity) (Spruit et al., 2013).

3. Strength training including 7 exercises (2 sets of 10 repetitions) of the major upper and lower limb muscle groups using free weights and ankle weights (15 min) (American College of Sports Medicine, 2009). The amount of weight was

between 50 and 85% of the 10-repetition maximum (10-RM) (Spruit et al., 2013). The training progression was based on the two-for-two rule (load was increased when 2 additional repetitions could be performed on 2 consecutive sessions) (American College of Sports Medicine, 2009) and on the patient's symptoms (modified Borg scale 4-6) (Spruit et al., 2013).

4. Balance training consisting of static and dynamic exercises using upright positions (5 min).

In the psychoeducation component, the main themes addressed were information about COPD, medication management, healthy lifestyles, falls and their prevention, emotion-management strategies, and community resources.

## Data Collection

Sociodemographic and clinical (smoking habits, body mass index, exacerbations in the past 3 months) data were obtained to characterize the sample. Data on lung function, dyspnea, functional balance, muscle strength, exercise tolerance, emotional state, and HRQOL were collected before and after the PR program. All questionnaires/tests were administered in a standardized order.

## Outcome Measures

## Lung function

A spirometric test using a portable spirometer (MicroLab 3500, CareFusion, San Diego, California), was performed according to standardized guidelines (Miller et al., 2005).

## Dyspnea

Patients reported their activity limitations resulting from dyspnea by selecting the statement from the Modified Medical Research Council questionnaire that best described their limitations (Vestbo et al., 2013). The questionnaire comprises 5 grades (statements) in a scale from 0 to 4, with higher grades indicating greater perceived respiratory limitation. This scale is simple and valid to characterize the impact that dyspnea has on activities of patients with

COPD (Vestbo et al., 2013) and variations of one point indicate a perceived clinical improvement (de Torres et al., 2002).

## Functional balance

The Timed Up and Go test was used to assess functional balance (Podsiadlo & Richardson, 1991). The test requires the patient to rise from a standard chair, walk 3 m, turn around, walk back to the chair, and sit down. Patients were instructed to walk quickly but as safely as possible. Two tests were performed, and the best performance was considered.

## Muscle strength

The muscle strength of the shoulder flexors and of the knee extensors of the dominant limbs was assessed using the 10-RM with ankle and free weights. In patients with COPD, the completion of 1-RM testing may not be advisable or safe (Lotshaw, Thompson, Sadowsky, Hart, & Millard, 2007); thus, 10-RM has been used (Reynolds, Gordon, & Robergs, 2006). The 10-RM was considered the maximum amount of weight that could be moved through the full range of motion 10 times with the proper technique and without compensatory movements (American College of Sports Medicine, 2009).

## Exercise tolerance

Exercise tolerance was measured using the 6MWT. The measurement properties of this test are well established in COPD, and it has showed a similar peak rate of oxygen uptake and heart rate as an incremental cycle ergometer test (Hill et al., 2012). Two tests were performed according to the protocol described by the American Thoracic Society (American Thoracic Society, 2002), and the best performance was considered. The minimum clinically important difference for the 6MWT is 25 m in patients with COPD (Holland et al., 2010).

# **Emotional state**

The Depression, Anxiety, Stress Scales (DASS) measure the negative emotional states of depression, anxiety, and stress (Moradipanah, Mohammadi, & Mohammadil, 2009). Each subscale has 7 items, and the participant is asked to use a 4-point (from 0 to 3) severity scale to rate the extent to which they have experienced each state over the past week. Internal consistency has been shown to be acceptable for all 3 scales (Cronbach's alpha statistics between 0.82 and 0.93) (Henry & Crawford, 2005). Consistent with convention, during the statistical analysis, all DASS-21 scores were doubled. This procedure facilitates comparison with normative values established for DASS-42. The maximum score of DASS-42 is 42 in each of depression, anxiety and stress scales, and higher scores indicate high levels of emotional distress.

## HRQOL

The St George Respiratory Questionnaire (SGRQ) is a disease-specific instrument designed to measure quality of life in patients with chronic lung disease (Jones, 2005). The questionnaire has 3 domains: symptoms, activities, and impact. SGRQ presented high internal consistency with Cronbach's alpha statistics (>0.7 in the sub-domains and >0.9 in the overall questionnaire) (Ferrer et al., 2002). For each domain and for the total questionnaire, the score ranges from 0 (no impairment) to 100 (maximum impairment). A change of 4 units is considered clinically relevant (Jones, 2005).

## Statistical Analysis

Using 6MWT data from the study of Riario-Sforza et al (effect size [ES]=0.88) (Riario-Sforza et al., 2009), a sample size estimation with 95% power ( $\alpha$ =0.05) was performed. This power analysis determined that a statistically significant difference in 6MWT after a PR program would be detected with 19 subjects. As PR programs have considerable dropout rates, varying between 20 and 40% (Fischer et al., 2009; Garrod, Marshall, Barley, & Jones, 2006), 30 patients were recruited.

Descriptive statistics were used to describe the sample. For each outcome measure, the normality of the data was investigated with the Shapiro–Wilk test. Paired t tests for normally distributed data and Wilcoxon signed-rank tests for ordinal/non-normally distributed data were used to compare pre- and post-PR

variables. The level of significance was set at 0.05. These analyzes were performed using IBM SPSS Statistics 20.0 (IBM Corporation, Armonk, New York).

Statistical analysis was completed with the estimation of ES indices, which evaluate the magnitude of treatment effect (Kraemer & Kupfer, 2006). The formula Cohen's dz was used (mean change score divided by the SD of change), as this is the ES index recommended for matched pairs (Faul, Erdfelder, Lang, & Buchner, 2007). Cohen's dz for each outcome measure was calculated using the G\*Power 3 software (University Düsseldorf, Düsseldorf, Germany) and was interpreted as a small ( $\geq$  0.2), medium ( $\geq$  0.5), or large ( $\geq$  0.8) effect (Cohen, 1988).

## Results

Thirty patients enrolled in the study; however, 4 (13.3%) dropped out due to overlap between the program schedule and professional activities (n=1), relocation (n=1), respiratory exacerbation (n=1) and no reason given (n=1). Therefore, 26 participants (16 males; age 67.8  $\pm$  10.3 years old) completed the study. Table 1 provides the characteristics of the participants.

Characteristics	Result
Age, mean ± SD years	67.8 ± 10.3
Male, n (%)	16 (59.3)
BMI, mean $\pm$ SD kg/m <sup>2</sup>	28.7 ± 5.0
Smokers, n (%)	7 (25.9)
Exacerbations past 3 months, n (%)	
0	14 (53.9)
1-2	7 (26.9)
≥ 3	5 (19.2)
FEV1, mean ± SD L	$2 \pm 0.4$
$FEV_1$ , mean ± SD % of predicted	83.8 ± 5.4
n = 26 BMI = body mass index	

Table 1. Sociodemographic and clinical characteristics of the participants

The PR program had no effect on lung function (pre 83.8% of predicted vs post 84.1% of predicted, p=.73) (Table 2). A reduction in participants' dyspnea was observed (pre median [interquarlile range] 1[1-2] vs post 1[0-1], p=.003; ES=0.7), with more than half of the participants (n=16; 61.5%) presenting a Modified Medical Research Council scale variation > 1. Significant improvements were also verified in functional balance (pre 7.8 s vs 6.7 s, p<.001), muscle strength (shoulder flexors pre 2.3 kg vs post 3.6 kg, knee extensors pre 4.1 kg vs post 6.7 kg, p<.001) and exercise tolerance (pre 432 m vs post 464 m, p<.001), with medium and large ES values (from 0.5 to 1.3) (Table 2). However, no differences were found for the emotional states of depression (pre median 6 vs post 4, p=.65), anxiety (pre median 6 vs post 5; p=.82), and stress (pre median 10 vs post 8, p=.63). The SGRQ total score (pre 31.3 vs post 25, p=.005; ES=0.3), the SGRQ symptom score (pre 46.3 vs post 34.7, p<.001; ES=0.6) and the SGRQ activity score (pre 44 vs post 34.8, p=.02; ES=0.4) improved significantly after PR, reaching the minimum clinically important difference (4 units) (Jones, 2005). However, there was no significant improvement on the SGRQ impact score (pre 19.4 vs post 16.3, p=.14).

Table 2.	Effect	of PR	on	lung fun	ction,	dyspnea,	functional	balance,	muscle	strength,	exercise
tolerance	e, emot	ional s	tate	, and he	alth-re	elated qua	lity of life				

Variable	Pre-PR	Post-PR	р	ES
$FEV_1$ , mean ± SD % of predicted	83.8 ± 6.4	84.1 ± 5.4	.73†	0
MMRC questionnaire score (median	1 (1-2)	1 (0-1)	.003 <sup>‡</sup>	0.7
[interquartile range])				
TUG score, mean ± SD s	7.8 ± 1.5	6.7±1.2	<.001 <sup>†</sup>	0.8
10-RM shoulder flexor strength, mean $\pm$ SD kg	$2.3 \pm 0.9$	3.6 ± 1.2	<.001 <sup>†</sup>	1.2
10-RM knee extensor strength, mean $\pm$ SD kg	4.1 ± 2.1	6.7 ± 1.9	<.001 <sup>†</sup>	1.3
6MWD, mean ± SD m	432 ± 76	464 ± 76	<.001 <sup>†</sup>	0.5
DASS score (median [interquartile range])				
Depression	6 (1.5-9)	4 (0.5-8)	.65 <sup>‡</sup>	0.2
Anxiety	6 (1.5-12)	5 (2-10)	.82 <sup>‡</sup>	0
Stress	10 (5.5-16)	8 (4-15)	.63 <sup>‡</sup>	0
SGRQ, mean ± SD				
Total score	31.3 ± 18.5	25 ± 17.8	.005†	0.3
Symptom score	46.3 ± 20.2	34.7 ± 21.4	<.001 <sup>†</sup>	0.6
Activity score	44 ± 25.2	34.8 ± 24.3	.02†	0.4
Impact score	19.4 ± 17.9	16.3 ± 15.4	.14†	0.2
n = 26 <sup>†</sup> Paired t test <sup>‡</sup> Wilcoxon signed-rank test PR= pulmonary rehabilitation ES= effect size MMRC= Modified Medical Research Council TUG= Timed Up and Go 10-RM= 10-repetition maximum 6MWD= 6-min walking distance DASS= Depression, Anxiety and Stress Scales SGRQ= St George Respiratory Questionnaire.

# Discussion

According to our knowledge, this was the first study to investigate the effects of PR on different health domains in patients with mild COPD. The main finding was that a 12-week PR program was effective in improving subjects' dyspnea, functional balance, muscle strength, exercise tolerance, and HRQOL.

A perceived clinical improvement in dyspnea was observed in > 50% of the patients, in line with the existing evidence on the benefits of PR in patients with moderate-to-very-severe COPD (de Torres et al., 2002). This result demonstrates that patients with mild COPD already experience restrictions in their daily life due to dyspnea and that PR has the potential to reverse this situation. Regarding the effect of the program on subjects' functional balance, a change of  $-1.1 \pm 1$  s in the Timed Up and Go score was found. This change is lower than that obtained by Beauchamp et al (-1.5  $\pm$  2.4 s), who examined the effect of a standard PR program on the balance of patients with more severe COPD grades (mean FEV1 46.3 ± 22.3%) (Beauchamp, O'Hoski, Goldstein, & Brooks, 2010). However, this result is not surprising since subjects with mild COPD had better baseline scores compared with patients included in the previously mentioned study, and thus, less potential to further improve their functional balance was expected. Respective increases of 56.5 and 63.4% in shoulder flexor and knee extensor muscle strength were verified. These results are difficult to interpret in the absence of published information on minimum clinically important differences for the 10-RM. Nevertheless, the percentage changes found are similar to previous research (a 56.3% increase in chest pull exercise and 88.2% in leg extension) (Ortega et al., 2002).

The improvement in the distance walked after PR was ~32 m. Considering that 25 m is the minimum clinically important difference for the 6MWT in patients with COPD (Holland et al., 2010), it could be assumed that this study achieved the clinically important effect. However, this minimum clinically important difference was established based on a sample of patients with a wide range of disease severity and may not represent a clinically important effect for patients with mild COPD. Future studies should determine the minimum clinically important difference for the 6MWT in patients with mild COPD to contribute to clinical decision making in this COPD population.

An improvement in the SGRQ total score of ~6 units was also observed, exceeding the 4 units considered clinically relevant (Jones, 2005). This result demonstrates that HRQOL in patients with mild COPD, even if not severely affected (baseline scores of 31.3 in 100), can be improved with PR. Contrary to the symptom and activity domains, the impact domain was not significantly different after PR. Patients with mild COPD might not yet experience relevant disturbances in social and psychological functioning in their daily life, demonstrated by the low impact scores found at baseline (19.4 in 100) (Shrikrishna et al., 2012), and therefore, this domain had less potential to be improved.

The PR program had no effect on lung function, which is in accordance with the short-term effects of PR (Zwick et al., 2009). However, a longitudinal study with patients with moderate-to-severe COPD showed that, after 3 y, the decline in FEV<sub>1</sub> was significantly lower in the PR group compared to the standard care group (Stav, Raz, & Shpirer, 2009). The potential of PR in delaying the decline of lung function should therefore be examined in patients with mild COPD as well. Patients' emotional state also did not improve after the intervention. However, significant benefits in the emotional function of patients with moderateto-very-severe COPD after PR programs have been described (Lacasse et al., 2006). Since subjects' baseline scores in DASS were only slightly higher than normative values (depression 6 vs 2, anxiety 6 vs 2, stress 10 vs 8) (Henry & Crawford, 2005), one possible reason for this result may be that patients with mild COPD may not yet experience significant emotional distress.

The overall findings suggest that PR is effective in improving dyspnea, functional balance, muscle strength, exercise tolerance, and HRQOL in patients with mild COPD. Thus, the critical question for future studies should move from "should patients with mild COPD be integrated in PR?" to "how should PR be delivered to these patients?". Since patients are not referred to hospital-based PR programs until they have advanced COPD (Spruit et al., 2013), less expensive and complex PR programs available at primary care centers could be a promising strategy to deliver PR to patients with mild COPD. Through the exercise training component, these programs would maintain patients at higher levels of function. Exercise programs in fitness centers with adequate supervision by trained professionals would probably accomplish the same physical benefits of these simple PR programs with fewer costs; however these programs do not address patients' education and behavior change needs. Through collaborative self-management strategies, the psychoeducation component of PR increases patients' knowledge and skills, key aspects to optimally manage their disease. Therefore, the potential of primary care-based PR to modify the COPD trajectory in patients at earlier grades should be investigated in future COPD research.

This study has some limitations that need to be acknowledged. The absence of a control group is a limitation of this exploratory study. However, as no research has been conducted on this topic, this limitation does not appear to remove the validity and importance of the results found. In future studies, a control group of patients with similar sociodemographic and clinical characteristics should be included. A small sample size was estimated to be sufficient to detect statistically significant differences in the 6MWT; however, a larger sample would probably help detect statistically significant differences in the other outcome measures collected such as DASS and SGRQ impact score. Nonetheless, data from these outcome measures may inform the estimation of sample sizes in future studies. Moreover, the evaluators in this study were the

same health professionals that delivered the PR program, which may have influenced the way that outcome measures were assessed. Due to the crosssectional design, the long-term effects of PR on mild COPD could not be established. Blind randomized controlled trials with long-term follow-ups are therefore needed.

# Conclusion

The PR program was effective in improving dyspnea, functional balance, muscle strength, exercise tolerance, and HRQOL in patients with mild COPD, suggesting that these patients would benefit of being routinely included in PR programs. Studies with more robust designs and with long-term follow-ups are needed to inform guidelines for PR in mild COPD.

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Study II

Short- and long-term effects of pulmonary rehabilitation in patients with mild COPD: A comparison with patients with moderate-to-severe COPD

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#### Abstract

**Purpose:** Pulmonary rehabilitation (PR) is effective in patients with moderate-to-severe COPD. However, the effects of PR in patients with mild COPD have not yet been established. Thus, this study investigated the short- and long-term effects of PR in patients with mild COPD in comparison with patients with moderate-to-severe disease.

**Methods:** 32 patients with mild (Group 1) and 29 with moderate-to-severe (Group 2) COPD completed the study. Both groups participated in a 12-week PR program with exercise training and psychoeducation. Outcome measures at baseline, 3 (post-PR), 6 and 9 months included the 6-min walk test (6MWT); the Modified Medical Research Council questionnaire; 1-repetition maximum on the chest press and knee extension; the Brief physical activity assessment; number of exacerbations on the past 3 months and the St George Respiratory Questionnaire (SGRQ).

**Results:** Improvements in the 6MWT, chest press and knee extension and physical activity were observed post-PR (p<0.001), with no differences between the two groups. Reduction in the number of exacerbations (p<0.001) and improvements in the SGRQ total (p<0.001) were also observed, however, with greater magnitude in group 2 (p=0.029 and p<0.001). Excepting peripheral muscle strength, all the achieved benefits were sustained at 6 and 9 months (p>0.05).

**Conclusions:** PR improves exercise tolerance, muscle strength, physical activity and health-related quality of life and reduces exacerbations in patients with mild COPD as in patients with moderate-to-severe COPD. Moreover, most of these benefits were maintained at 9 month follow-up, suggesting that PR could be part of the management of mild COPD.

#### Introduction

Chronic obstructive pulmonary disease (COPD) is a highly incapacitating disease (Hilleman, Dewan, Malesker, & Friedman, 2000; Miravitlles, Murio, Guerrero, & Gisbert, 2003). Patients with mild COPD already present impairments in quadriceps muscle strength, health-related quality of life (HRQOL) and physical activity levels (Maltais, Dennis, & Chan, 2013; Shrikrishna et al., 2012), that tend to worsen over time (Maltais et al., 2013).

Pulmonary rehabilitation (PR) is effective in improving dyspnea and HRQOL (Lacasse, Goldstein, Lasserson, & Martin, 2006), and it is recognized as a core component of the management of patients with moderate-to-severe COPD (Spruit et al., 2013). In patients with mild COPD, however, the disease-modifying potential of PR is not yet established. This has been identified by the 2013 American Thoracic Society/European Respiratory Society official statement on PR as a major research topic to be addressed (Spruit et al., 2013). From the studies available, PR appears to improve exercise tolerance and HRQOL of patients with mild COPD (Jácome & Marques, 2014a; Riario-Sforza et al., 2009). Nevertheless, these studies were only focused on the short-term effects of PR (Jácome & Marques, 2014b). Long-term studies are needed to determine the effectiveness of PR in this group of patients.

In patients with moderate-to-severe COPD, it has been shown that in the absence of any maintenance strategy, benefits of PR diminish over 6-12 months (Griffiths et al., 2000). Reasons for this decline are multifactorial, comprising decreased adherence to exercise, progression of the disease and exacerbations (Bestall et al., 2003; Heppner, Morgan, Kaplan, & Ries, 2006). Patients with mild COPD may benefit equally from PR and its benefits may also decrease over time. However, this has not yet been explored.

Thus, this study investigated the short- and long-term effects of PR in patients with mild COPD in comparison with patients with moderate-to-severe COPD.

# Methods

#### Design and Participants

A non-experimental, prospective two-arm longitudinal study was conducted. Outpatients with COPD were recruited from two community primary care centers. Inclusion criteria were diagnosis of mild, moderate or severe COPD (Vestbo et al., 2013), age  $\geq$  40 years old, and clinical stability (i.e., 1 month without hospital admissions or exacerbations) (Vestbo et al., 2013). Patients were excluded if they presented severe psychiatric, neurologic or musculoskeletal conditions (Nici & ZuWallack, 2010) and/or unstable cardiovascular disease that could interfere with their performance during exercise training. The study was approved by the Center Health Regional Administration and from the National Data Protection Committee. Eligible patients, identified via clinicians, were contacted by the researchers, who explained the purpose of the study. Written informed consent was obtained prior to data collection.

#### Intervention

A 12-week PR program was delivered in a community primary-care center by three physical therapists. This program, described in detail elsewhere, was composed of 3 weekly sessions of exercise training (60 min) and 1 weekly session of psychoeducation (90 min) (Jácome & Marques, 2014a). Each session of exercise training comprised of five components: warm up, endurance training, strength training, balance training and cool down. Patients with mild and with moderate-to-severe COPD trained together, which ensured a uniform training. In addition, it enabled the sharing of experiences among patients with different disease severities. At the end of PR, all patients were advised to continue exercising at home.

# Data Collection

Socio-demographic, anthropometric and clinical data were first obtained. Spirometry (MicroLab 3500, CareFusion, Kent, UK) was then performed (Miller et al., 2005). Patients were classified using the Global Initiative for Chronic Obstructive Lung Disease (GOLD) combined assessment (Modified Medical Research Council questionnaire (mMRC), spirometric classification and history of exacerbations in the previous year) (Vestbo et al., 2013). Exercise tolerance, dyspnea, self-reported physical activity, history of exacerbations, HRQOL and peripheral muscle strength were assessed in a standardized order at baseline (pre-PR), and 3 (post-PR), 6 and 9 months later.

#### Feasibility measures

Feasibility was assessed by adherence to PR sessions, number/reasons of dropouts and number of adverse events.

#### Outcome Measures

Primary outcome

Exercise tolerance was measured using the 6-min walk test (6MWT). The measurement properties of this test are well established in COPD (Hill et al., 2012). Two tests were performed according to international guidelines (American Thoracic Society, 2002) and the best performance was considered. The minimal important difference for the 6MWT is 25 meters (Holland et al., 2010).

#### Secondary outcomes

Dyspnea

Patients reported their activities limitation resulting from dyspnea by selecting one statement of the mMRC (Vestbo et al., 2013). The questionnaire comprises five grades (0-4), with higher grades indicating greater perceived respiratory limitation. Variations of 1 indicate a perceived clinical improvement (de Torres et al., 2002).

# Peripheral muscle strength

Muscle strength of the major muscle groups of the chest, shoulders and thighs were determined by the 1 repetition maximum (1-RM) (American College of Sports Medicine, 2009) in chest press and knee extension exercises (Multigym Plus G112X, Vitoria-Gasteiz, ES).

# Self-reported physical activity

The brief physical activity assessment was used as it is reliable (Marshall, Smith, Bauman, & Kaur, 2005) and recommended to assess physical activity in COPD (Royal Dutch Society for Physical Therapy, 2008). It consists of two questions (score 0-4) about the frequency and duration of vigorous/moderate intensity physical activity undertaken in a "usual" week (Marshall et al., 2005). The total score is obtained from the sum of the two questions. Score < 3 means that patient is insufficiently active and  $\geq$  4 that is sufficiently active (Marshall et al., 2005).

## History of exacerbations

Patients were asked about the number of exacerbations in the preceding 3 months (Guell et al., 2000; Rubí et al., 2010). Patients were explained what was an exacerbation using the current standardized definition (Rodriguez-Roisin, 2000).

#### Health-related quality of life

The St George Respiratory Questionnaire (SGRQ) was used (Jones, 2005). The questionnaire has three domains: symptoms, activities and impact. The SGRQ presented high internal consistency with Cronbach's alphas of .770 in the symptoms domain, .740 in the activities domain, .634 in the impact domain and of .830 in the overall questionnaire. Score ranges from 0 (no impairment) to 100 (maximum impairment). A change of 4 units is considered clinically relevant (Jones, 2005).

## Statistical Analysis

Using G\*Power 3.1 (University Düsseldorf, Düsseldorf, DE), it was determined that 19 patients with mild COPD were required to yield 95% power ( $\alpha$ =0.05) to detect a statistically significant difference in 6MWT using an effect size of 0.88 (Riario-Sforza et al., 2009). However, 40 patients were recruited to increase the power to detect changes in the secondary outcome measures and to compensate for the 20-40% expected dropouts (Fischer et al., 2009; Garrod,

Marshall, Barley, & Jones, 2006). The same number of patients with moderateto-severe COPD was recruited.

Descriptive statistics were used to describe the sample. Differences i) between completers and dropouts in each group at each time point, and ii) between patients with mild and moderate-to-severe COPD at baseline were tested using independent t-tests for continuous normally distributed data, Mann-Whitney U tests for continuous non-normally distributed data and chi-square tests for categorical data.

Two-way analysis of variance with repeated measures was used to establish the significant effects of time, group and these factors in combination (Elliott & Woodward, 2007). The effect size was computed via Partial eta-squared as it is the index more commonly reported in the analysis of variance (Levine & Hullett, 2002). Partial eta-squared ( $\eta^2$ ) was interpreted as small ( $\geq 0.01$ ), medium ( $\geq 0.06$ ) or large ( $\geq 0.14$ ) (Cohen, 1969). When the effect of time was significant, post hoc analyzes were conducted with pairwise comparisons using the Bonferroni correction. When the effect of group was significant, a one-way analysis of variance with repeated-measures and pairwise comparisons using Bonferroni correction were performed.

Statistical analyzes were performed using IBM SPSS Statistics version 20.0 (IBM Corporation, Armonk, NY, USA) and plots created using GraphPad Prism version 5.01 (GraphPad Software, Inc., La Jolla, CA, USA). The level of significance was set at 0.05.

# Results

Participants

A total of 61 completed the study (Figure 1).



Figure 1. Participant flow diagram throughout the study

For each group, there were no significant differences between completers and dropouts at any time point (p>0.05). Participants from both groups were similar at baseline, with the exception of lung function, GOLD combined assessment, physical activity and SGRQ (p<0.05) (Table 1). None of the patients used long-term oxygen therapy or needed supplemental oxygen during exercise training.

Characteristics	Mild	Moderate-to-severe	p-value
	COPD	COPD	
	(n=32)	(n=29)	
Age (yrs)	65.9 ± 8.9	65.5 ± 9.8	.853
Male	22 (68.8%)	24 (82.8%)	.113
BMI (kg/m²)	$28.4 \pm 4.6$	29.6 ± 4.5	.347
Smoking status			
Current smokers	12 (37.5%)	7 (24.1%)	.109
Former smokers	16 (50%)	13 (44.8%)	.887
Never smokers	4 (12.5%)	9 (31.1%)	.054
FEV1 (L)	$2.2 \pm 0.5$	1.5 ± 0.5	<.001
FEV <sub>1</sub> (% predicted)	86.7 ± 5.2	55.4 ± 16.7	<.001
FEV <sub>1</sub> /FVC (%)	66.4±6.0	58.9±11.9	.002
GOLD combined assessment			
A – low risk, less symptoms	23 (71.9%)	9 (31%)	.002
B – low risk, more symptoms	6 (18.8%)	4 (13.8%)	
C – high risk, less symptoms	1 (3.1%)	9 (31%)	
D – high risk, more symptoms	2 (6.2%)	7 (24.2%)	
6MWT	473.5 ± 73.3	447.6 ± 80.8	.202
mMRC	$1.3 \pm 0.9$	1.6 ± 0.8	.105
Chest press (kg)	31.9 ± 10.5	31.6 ± 9.6	.917
Knee extension (kg)	41.6 ± 15.7	$39.9 \pm 9.4$	.653
Physical activity	2.4 ± 2.1	1.1 ± 1.4	.009
Exacerbations past 3 months	0.8 ± 1.3	1.6 ± 1.6	.051
SGRQ total	28.0 ± 16.9	45.2 ± 16.4	<.001
SGRQ symptoms	41.3 ± 21.4	55.0 ± 19.2	.013
SGRQ activities	41.1 ± 22.8	59.8 ± 15.5	.001
SGRQ impact	16.3 ± 14.7	33.9 ± 19.7	<.001
Data are presented as mean±SD or n(%).			

#### Table 1. Characteristics of the participants at baseline

BMI, body mass index; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global initiative for chronic Obstructive Lung Disease; 6MWT, 6-minute walk test; mMRC, Modified Medical Research Council questionnaire;

SGRQ, St. George's Respiratory Questionnaire

# Feasibility

No significant differences between groups were observed in exercise training (mild 80±11% vs moderate-to-severe 76±14%, p=0.226) or psychoeducation (mild 90±13% vs moderate-to-severe 92±9%, p=0.439) adherence. Dropouts were similar in both groups, with rates of 20 and 27.5% (p=0.300). No adverse events were reported.

# Primary outcome

Figure 2 summarizes the results of the 6MWT over the 4 time points. There was no effect for group (p=0.170) nor significant interaction between time and group (p=0.883), but a significant effect for time was found (p<0.001;  $\eta^2$ =0.419). Exercise tolerance increased significantly immediately after PR (p<0.001), with most participants achieving a clinical meaningful improvement (mild 68.8%, moderate-to-severe 70.4%, p=0.560) (Table 2). These improvements were maintained at 6 and 9 months (Figure 2, Table 3).



Figure 2. 6-min walking distance from baseline to 9 month follow-up in patients with mild COPD and patients with moderate-to-severe COPD. Data are presented as mean and standard error. \* p<0.001 from baseline to post pulmonary rehabilitation

Outcomes	Mean difference	Mean difference (baseline to 3 months)		
	Mild COPD	Moderate-to-severe COPD		
6MWD	-52.8 (-68.8→-36.8)	-49.7 (-64.5→-34.9)		
mMRC	0.6 (0.3→0.9)	0.1 (-0.2→0.5)		
Chest press (kg)	-10.0 (-13.2→-6.7)	<b>-11.1 (-13.7→-8.5)</b>		
Knee extension (kg)	<b>-</b> 18.5 ( <b>-</b> 24.9→-12.1)	-17.1 (-21.4→-12.8)		
Physical activity	-2.2 (-3.2→-1.2)	-3.5 (-4.3→-2.7)		
Exacerbations past 3 months	0.4 (0.1→0.7)	0.8 (0.2→1.4)		
SGRQ total	5.8 (2.2→9.5)	8.5 (3.9→13.0)		
SGRQ symptoms	7.6 (1.7→13.4)	11.1 (4.0→18.2)		
SGRQ activities	10.0 (3.4→16.5)	8.9 (2.5→15.3)		
SGRQ impact	2.8 (-0.6→6.2)	7.4 (1.8→12.9)		
Data are presented as mean difference (95%	confidence intervals).			

Table 2. Mean differences between baseline and 3 month follow-up (post-pulmonary rehabilitation).

6MWD, 6-min walk distance; mMRC, Modified Medical Research Council questionnaire;

PR, pulmonary rehabilitation; SGRQ, St George Respiratory Questionnaire.

Secondary outcomes

For all secondary outcomes, the interaction between time and group was not significant (p>0.05), with the exception of history of exacerbations (p=0.029). mMRC showed an effect for time (p=0.001;  $\eta^2$ =0.090) and for group (p=0.005;  $\eta^2$ =0.135). Post hoc analysis revealed that mMRC changed significantly in participants with mild COPD across time (p<0.001;  $\eta^2$ =0.184). In this group, dyspnea decreased after PR (MD=0.6; p<0.001) (Table 2), but at 6 (MD=-0.3, p=0.006) and 9 (MD=-0.4, p=0.003) months this improvement was not sustained (Table 3). No significant differences in mMRC were observed in participants with moderate-to-severe COPD (p=0.205).

Significant differences were found over time for the chest press, knee extension and physical activity (p from <0.001 to 0.029;  $\eta^2$  from 0.1 to 0.463), nevertheless, there were no differences between groups (p>0.05). These improvements were observed after PR (p from <0.001 to 0.010, Table 2) and sustained at 6 and 9 months for physical activity, but not for chest press (all p<0.002) and knee extension (all p<0.001) (Table 3). The number of exacerbations significantly decreased from baseline to 6 months in both groups (p=0.001). At 6 and 9 months, the number of exacerbations was not significantly different from the number observed after PR. However, the significant interaction found (p=0.029), showed that participants with moderate-to-severe COPD had a higher reduction in the number of exacerbations (Table 3).

Outcome	Mean difference (3 months to 6 months)		Mean difference (3 months to 9 months)		
	Mild	Moderate-to-severe	Mild	Moderate-to-severe	
	COPD	COPD	COPD	COPD	
6MWD	8.6 (-2.8→20.0)	2.3 (-13.4→18.1)	13.2 (2.9→23.6)	14.1 (-1.9→30.1)	
mMRC	-0.3 (-0.6→-0.1)	0.1 (-0.2→0.4)	-0.4 (-0.7→-0.1)	0.1 (-0.2→0.4)	
Chest press (kg)	3.6 (0.4→6.7)	3.2 (0.9→5.6)	5.3 (2.7→7.9)	5.4 (2.7→8.2)	
Knee extension (kg)	4.5 (0.5→8.4)	7.9 (4.2→11.5)	9.9 (4.9→15.0)	10.7 (6.4→15.0)	
Physical activity	1.0 (0.1→1.9)	1.0 (0.0→1.9)	0.4 (-0.4→1.3)	0.3 (-0.8→1.4)	
Exacerbations past 3	0.0 (-0.3→0.3)	0.1 (-0.3→0.5)	-0.3 (-0.7→0.2)	0.2 (-0.2→0.6)	
months					
SGRQ total	2.0 (-1.1→5.0)	2.8 (-2.1→7.7)	4.5 (0.5→8.5)	3.3 (-1.1→7.6)	
SGRQ symptoms	6.9 (-1.2→15.0)	-0.6 (-8.8→7.5)	14.0 (5.6→22.4)	3.3 (-5.4→11.9)	
SGRQ activities	3.4 (-6.9→13.6)	10.9 (0.1→21.7)	-0.4 (-6.4→5.5)	2.9 (-2.5→8.3)	
SGRQ impact	-1.4 (-5.9→3.2)	4.6 (-4.7→14.0)	-2.4 (-8.2→3.4)	3.7 (-0.8→8.1)	
Data are presented as mean difference (95% confidence intervals).					

Table 3. Mean differences between the 3 month follow-up (post-pulmonary rehabilitation) and the 6 and 9 month follow-ups

6MWD, 6-min walk distance; mMRC, Modified .Medical Research Council questionnaire;

SGRQ, St George Respiratory Questionnaire.

For the SGRQ total and domains scores, there was a significant difference between groups (p from <0.001 to 0.002; n<sup>2</sup> from 0.161 to 0.236) and over time (p from <0.001 to 0.016;  $\eta^2$  from 0.061 to 0.304). Figure 3a shows the SGRQ total score over time. After PR, the magnitude of improvement in SGRQ total score was greater in participants with moderate-to-severe COPD (MD=8.5; p=0.006) than the improvement in participants with mild COPD (MD=5.8; p=0.016) (Table 2). Nevertheless. most participants achieved a clinically meaningful improvement, with no differences between groups (mild 65.6% and moderate-tosevere 77.8%; p=0.392). In the symptoms domain, both groups improved from baseline to post-PR (p=0.013 and p=0.003), but participants with mild COPD had a further improvement from post-PR to 9 months (p=0.002) (Figure 3b). Improvements in the activity domain were observed in both groups, however, they were greater in participants with moderate-to-severe COPD than in those with mild COPD ( $\eta^2$ =0.196 vs.  $\eta^2$ =0.106) (Figure 3c). Improvements in the impact domain where only seen in participants with moderate-to-severe COPD (p=0.010;

PR, pulmonary rehabilitation;

 $\eta^2$ =0.144) (Figure 3d). The benefits of PR in SGRQ total and domains scores were sustained at 6 and 9 months in both groups (Table 3).



Figure 3. St George Respiratory Questionnaire total (a) and domain (b, c, d) scores from baseline to 9 month follow-up in patients with mild COPD and patients with moderate-to-severe COPD. Data are presented as mean and standard error. \* p<0.001 from baseline to post pulmonary rehabilitation, # p=0.002 from post pulmonary rehabilitation to 6 months.

# Discussion

This was the first study to assess the short- and long-term effects of PR in patients with mild COPD in comparison with patients with moderate-to-severe COPD. The main findings suggest that PR is effective in improving exercise tolerance, peripheral muscle strength, physical activity, HRQOL and in reducing the number of exacerbations in patients with mild COPD as well as in patients with moderate-to-severe COPD. Moreover, most of the achieved benefits were maintained at 9 month follow-up. The magnitude of the benefits were substantial and similar to other interventions (smoking cessation (Tønnesen, Mikkelsen, & Bremann, 2006), pharmacological interventions (Johansson et al., 2008;

Kanehara et al., 2008)) that are recommended for mild COPD. In addition, it was found that PR is as feasible for mild COPD as for moderate-to-severe disease.

The 6MWT improvement in patients with mild COPD was similar to that found in patients with moderate-to-severe COPD and it is in line with the range of values found in previous studies (34-60 meters) (Beauchamp, Francella, Romano, Goldstein, & Brooks, 2013; Egan et al., 2012; Spencer, Alison, & McKeough, 2010). Moreover, the increase was above the established minimal clinically important difference for the 6MWT (Holland et al., 2010). Nevertheless, exercise tolerance tended to decrease from post-PR to the end of the follow-up period in both groups (Bestall et al., 2003; Egan et al., 2012). The decline in the 6MWT raises the question of whether there are strategies that could promote longer lasting improvements (e.g., maintenance programs, telephone follow-up; feedback on physical activity levels). A recent study demonstrated that benefits of PR could be maintained in patients with moderate-to-severe COPD up to 1-year with a community-based maintenance exercise program supervised by fitness instructors (Beauchamp et al., 2013). This approach may also be feasible for patients with mild COPD and thus it should be explored in future research.

Dyspnea improved significantly with PR (de Torres et al., 2002), yet this benefit was not observed in patients with moderate-to-severe COPD, contradicting earlier studies (Beauchamp et al., 2013; Ortega et al., 2002). These differences may be due to the properties of the instruments used. In the present study, dyspnea was assessed with the mMRC, whereas in previous literature the Chronic Respiratory Disease Questionnaire was used (Beauchamp et al., 2013; Ortega et al., 2002). The mMRC, due to its limited number of levels, may have not been sensitive enough to detect small changes in patients with more advanced grades of the disease (Crisafulli & Clini, 2010). The Chronic Respiratory Disease Questionnaire, however, allows the symptoms to be expressed in a graduated scale (Guyatt, Berman, Townsend, Pugsley, & Chambers, 1987), which may be more adequate to detect small changes. Future

studies could investigate the sensitivity of the Chronic Respiratory Disease Questionnaire dyspnea domain to assess the impact of PR in mild COPD.

In line with previous studies (Margues et al., 2015; Spruit, Gosselink, Troosters, De Paepe, & Decramer, 2002), PR resulted in improvements in peripheral muscle strength. But after the initial improvement, losses similar to those described in the literature were observed (Ortega et al., 2002). Compared to baseline, at 3, 6 and 9 months, the percentage of patients sufficiently active increased (from 11-38% to 56-82%). However, care must be taken when interpreting this finding as patients' estimations of time spent in physical activities have been shown to be inaccurate compared with objective quantification (e.g., motion sensors) (Pitta, Troosters, Spruit, Decramer, & Gosselink, 2005). Nevertheless, in the present study, the brief physical activity assessment was used and it has been demonstrated that simple questionnaires, with an interval response option, have high coefficients of reliability and validity (Bonnefoy et al., 2001). Moreover, subjective methods have practical value mainly in providing the patients' view on their performance in activities of daily living (Pitta et al., 2006). Thus, the self-reported improvements in physical activity, even if not reflecting a true change, may reflect the importance of PR for increasing patients' awareness of their physical activity levels. A decline in number of exacerbations after PR was also found, which was sustained at 9 months. Nonetheless, this benefit was more marked in patients with moderate-to-severe COPD (Guell et al., 2000; Rubí et al., 2010).

The improvement in SGRQ exceeded the established minimal important difference and was sustained at 9 month follow-up (Jones, 2005). Previous studies in patients with moderate-to-very-severe COPD reported similar results (Bestall et al., 2003; Egan et al., 2012; Karapolat et al., 2007; Spencer et al., 2010). In addition, from post-PR to 9 month follow-up, SGRQ symptoms domain continued to improve in patients with mild COPD, sustaining the clinical relevance.

The overall findings suggest that PR conducted in the community is beneficial for patients with mild COPD. According to a clinical practice guideline, PR should be prescribed for symptomatic individuals with a FEV<sub>1</sub><50% predicted, and could be considered for symptomatic or exercise-limited individuals with a FEV<sub>1</sub> ≥50% predicted (Qaseem et al., 2011). The present study shows, however, that patients with mild COPD benefit from PR. Thus, despite the relevance of  $FEV_1$  in diagnosing COPD, it may be valuable to rethink the inclusion of  $FEV_1$  as a criterion for PR selection. Furthermore, the high adherence showed that PR was feasible and well tolerated in this group of patients. Community-based programs could be a novel approach to deliver PR to patients with mild COPD at a modest cost and using the existing community resources. Future research should assess the cost-effectiveness of this approach compared to standard care prior to broader implementation. Nevertheless, results also demonstrate that, similarly to what happens with patients with moderate-to-severe COPD, the benefits in patients with mild COPD start to decline after PR. This finding therefore points out to the importance of keeping patients motivated in changing behaviors after the program to maintain benefits. In patients with moderate-tosevere COPD, the benefits of PR have been shown to be maintained for up to 1year with a community-based maintenance exercise program, with minimal supervision from trained fitness instructors (Beauchamp et al., 2013). This method may also be effective in sustaining benefits in mild COPD and should be investigated in future research.

Some limitations need to be acknowledged. The absence of a control group is a limitation of this study. Inclusion of a group of patients with mild COPD receiving standard care would have strengthened the findings. Outcome assessment was also not blinded. Evaluators were the same physical therapists that delivered the program. Nevertheless, to minimize bias, the encouragement given by evaluators was standardized. This study had a follow-up period of 9 months. To assess the potential of PR to modify the disease trajectory in mild COPD, studies with longer follow-ups are recommended.

# Conclusions

PR is effective in patients with mild COPD as well as in patients with moderate-to-severe COPD. Moreover, most of the achieved benefits were maintained at 9 month follow-up. These data suggest that PR could be part of the management of mild COPD. Further work is warranted to determine the potential of PR to modify the disease trajectory in patients with mild COPD prior to a broader implementation.

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Study III

# Computerized respiratory sounds are a reliable marker in subjects with COPD

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#### Abstract

**Background:** Computerized respiratory sounds have shown potential in monitoring respiratory status in patients with COPD. However, variability and reliability of this promising marker in COPD are unknown. Therefore, this study assessed the variability and reliability of respiratory sounds at distinct air flows and standardized anatomic locations in subjects with COPD.

**Methods:** A 2-part study was conducted. Part 1 assessed the intra-subject reliability of respiratory sounds at spontaneous and target (0.4-0.6 and 0.7-1 L/s) air flows in 13 out-patients (69.3  $\pm$  8.6 y; FEV<sub>1</sub> of 70.9  $\pm$  21.4% of predicted). Part 2 characterized the inter-subject variability and intra-subject reliability of respiratory sounds at each standardized anatomic location, using the most reliable air flow, in a sample of 63 out-patients (67.3  $\pm$  10.4 y, FEV<sub>1</sub> of 75.4  $\pm$  22.9% of predicted). Respiratory sounds were recorded simultaneously at 7 anatomic locations (trachea and right and left anterior, lateral, and posterior chest). Air flow was recorded with a pneumotachograph. Normal respiratory sounds intensity and mean number of crackles and wheezes were analyzed with validated algorithms. Inter-subject variability was assessed with the intraclass correlation coefficient (ICC) and Bland-Altman plots.

**Results:** Relative reliability was moderate to excellent for normal respiratory sounds intensity and mean number of crackles (ICC of 0.66-0.89) and excellent for mean number of wheezes (ICC of 0.75-0.99) at the 3 air flows. Absolute reliability was greater at target air flows, especially at 0.4-0.6 L/s. Intersubject variability was high for all respiratory sound parameters and across locations (coefficient of variation of 0.12-2.22). Respiratory sound parameters had acceptable relative and absolute intra-subject reliability at the different anatomic locations. The only exception was the mean number of crackles at the trachea, for which both relative and absolute reliability were poor.

**Conclusions:** Respiratory sound parameters are more reliable at an air flow of 0.4-0.6 L/s and are reliable overall at all anatomic locations. This should be considered in future studies using computerized auscultation.

### Introduction

COPD is characterized by persistent air-flow limitation that is usually progressive (Vestbo et al., 2013). The FEV<sub>1</sub> has been established as the global marker for COPD diagnosis and monitoring(Vestbo et al., 2013). Nevertheless, changes in FEV<sub>1</sub> in response to treatment are small in relation to its repeatability (Calverley et al., 2003; Zwick et al., 2009). New clinical markers are therefore needed to evaluate the effectiveness of treatments for COPD (Jones & Agusti, 2006). These markers should be simple in terms of measurement, interpretation, and resources used, and should have acceptable reliability to ensure that the error involved in measurement is small enough to detect actual changes (Jones & Agusti, 2006).

Respiratory sounds are a simple, objective, and non-invasive marker to assess the function of the respiratory system (Bohadana, Izbicki, & Kraman, 2014) and do not require special resources beyond those typical of a patient– health professional encounter. However, variation and reliability of this promising marker in patients with COPD are still unknown.

Using computerized auscultation, it has been shown that adventitious respiratory sounds are characterized mainly by inspiratory crackles and expiratory wheezes in stable subjects with COPD (Bettencourt, Delbono, Spiegelman, Hertzmark, & Murphy, 1994; Jácome & Marques, 2015; Munakata et al., 1991; Murphy, 2008). Respiratory sounds have been suggested as useful in diagnosing community-acquired pneumonia in this population (Sánchez Morillo, Leon Jimenez, & Moreno, 2013). These studies showed that respiratory sounds may have potential to monitor the respiratory status of subjects with COPD. However, inter-subject variability and intra-subject reliability was not explored, hindering the interpretation of actual changes. In addition, respiratory sounds have been recorded without control of subjects' air flows, despite the well-known influence of air flow on respiratory acoustic and breathing pattern (Benchetrit, 2000; Gavriely & Cugell, 1996; Kraman, 1984).
Computerized respiratory sound analysis guidelines recommend recordings with inspiratory and expiratory peak air flows of 1–1.5 L/s or 10–15% of the predicted maximum peak expiratory air flow (Rossi et al., 2000). However, it is unknown if the air flow recommended suits the breathing pattern specificities of patients with COPD. It has been shown that breathing patterns of subjects with COPD have reduced complexity compared with healthy subjects (Dames, Lopes, & de Melo, 2014), which may affect respiratory sound reliability at different air flows. Computerized respiratory sound analysis guidelines also standardized 7 anatomic locations (trachea and right and left anterior, lateral, and posterior chest) to record respiratory sounds (Rossi et al., 2000). Nevertheless, intersubject variability and intra-subject reliability of respiratory sounds at each anatomic location in patients with COPD have not been investigated. To address these relevant research needs, this study assessed the (1) intra-subject reliability of breathing patterns and respiratory sounds at distinct air flows and (2) intersubject variability and intra-subject reliability of RS at each standardized anatomic location in subjects with COPD.

## Methods

#### Study Design

A 2-part study was conducted. Part 1 assessed the intra-subject reliability of breathing patterns and respiratory sounds at 3 distinct air flows using a small sample of out-patients with COPD. Part 2 characterized the inter-subject variability and intra-subject reliability of respiratory sounds at each anatomic location using the most reliable air flow from part 1 and a larger sample of outpatients with COPD.

#### Participants

Out-patients with COPD were recruited from 2 primary care centers. Inclusion criteria were diagnosis of COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria (presence of a postbronchodilator FEV<sub>1</sub>/FVC < 0.70)(Vestbo et al., 2013) and clinical stability for 1 month prior to the study (no hospital admissions, exacerbations as defined by the GOLD (Vestbo et al., 2013), or changes in medication for the respiratory system). Subjects were excluded if they had coexisting respiratory diseases or severe neurological, musculoskeletal, or psychiatric impairments. Approval for this study was obtained from the ethics committee of the Center Health Regional Administration (2013-05-02) and from the National Data Protection Committee (3292/2013). Eligible subjects were identified by clinicians and then contacted by the researchers, who explained the purpose of the study and asked about their willingness to participate. When subjects agreed to participate, an appointment with the researchers was scheduled. Written informed consent was obtained before data collection.

#### Data Collection

Sociodemographic, anthropometric (height and weight), and clinical (smoking habits, dyspnea, exacerbations in the past 3 months and in the previous year, medication) data were first recorded in the 2 study parts. Air flows and respiratory sounds were collected. Lung function was assessed by spirometry (MicroLab 3500, CareFusion, Kent, United Kingdom) according to standardized guidelines (Miller et al., 2005). Subjects were classified into 4 groups (A-D) using the GOLD combined assessment (Modified Medical Research Council scale, spirometry, and exacerbation risk) (Vestbo et al., 2013). All assessments were performed by 2 physiotherapists, and the order was standardized.

#### Part 1

Air flows and respiratory sounds were acquired simultaneously. Recordings were performed at spontaneous air flow, at a peak of 0.4-0.6 L/s (typical tidal air flow range), and at a peak of 0.7-1 L/s (modestly increased air flow). Similar target air flows have been used in previous research (Fiz, Gnitecki, Kraman, Wodicka, & Pasterkamp, 2008). After 5 min of quiet sitting, the 3 distinct air flows were acquired following the standardized order: spontaneous, 0.4-0.6 L/s, and 0.7-1 L/s. Spontaneous breathing was tested first so that it would not be influenced by the target air flows, and the order of the 2 target air flows was

selected based on increased air flow demand. Subjects were seated upright, wearing a nose clip, and breathing through a mouthpiece connected to a heated pneumotachograph (3830, Hans Rudolph, Shawnee, Kansas). For each air flow, subjects performed 3 trials of 20 s each (Vyshedskiy & Murphy, 2012), followed by a 2-min recovery period. During spontaneous air flow, subjects were instructed to breathe normally, and biofeedback of the flow signal was not presented. During target flows, subjects had visual biofeedback of the flow signal (RSS 100R research pneumotach system, Hans Rudolph) and were instructed to maintain the flow between 2 horizontal lines. The recording of each target flow was preceded by a training phase of at least 3 breathing cycles.

Respiratory sound recordings followed computerized respiratory sound analysis guidelines for short-term acquisitions (Rossi et al., 2000) and were performed simultaneously at 7 anatomic locations (trachea and right and left anterior, lateral, and posterior chest) (Sovijarvi, Vanderschoot, & Earis, 2000) using the LungSounds@UA interface (Pinho, Oliveira, Oliveira, Dinis, & Marques, 2014). Seven stethoscopes (Littmann Classic II S.E., 3M, St. Paul, Minnesota), with a microphone (frequency response between 20 Hz and 19 kHz - TOM-1545P-R, Projects Unlimited, Dayton, Ohio) and a preamplifier circuit (Intelligent Sensing Anywhere, Coimbra, Portugal) in the main tube were attached to the subject's skin with soft cloth surgical tape (3M). The analog sound signals were further amplified and converted to digital by an audio interface (ProFire 2626, M-Audio, Cumberland, Rhode Island). The signal was converted with a 24-bit resolution at a sampling rate of 44.1 kHz and recorded in WAV format.

## Part 2

Air flows and respiratory sounds were acquired simultaneously at the most reliable air flow identified in part 1. The same procedures from part 1 were followed.

## Signal Processing

All files were processed using algorithms written in MATLAB R2009a (Mathworks, Natick, Massachusetts). Breathing phases were automatically

detected using the positive and negative air flow signals. Mean inspiratory and expiratory times were then calculated. The mean air flows and tidal volumes (VT) were calculated per breathing phase using flow and volume raw signals. To combine the detected breathing phases with sound signals, the flow signals were time-synchronized with tracheal sound signals. Due to the simultaneous acquisition of respiratory sounds at the 7 locations, the breathing phases detected with tracheal sound sources.

Crackles were detected using a multi-algorithm technique based on established algorithms (Hadjileontiadis & Rekanos, 2003; Lu & Bahoura, 2008; Vannuccini, Rossi, & Pasquali, 1998). This multi-algorithm technique showed a 7% performance improvement over the best individual algorithm (Quintas, Campos, & Marques, 2013). Wheezes were detected using an algorithm based on time-frequency analysis (Taplidou & Hadjileontiadis, 2007). The mean number of crackles and wheezes per breathing phase was extracted. After excluding these adventitious sounds, normal respiratory sounds were analyzed based on the methodology proposed by Pasterkamp et al (1996) and the mean intensity was determined within a frequency band of 100 to 2,000 Hz (Pasterkamp et al., 1996; Sanchez & Vizcaya, 2003).

# Statistical Analysis

All statistical analyses were performed using SPSS 20.0 (IBM, Armonk, New York). The level of significance was set at 0.05.

# Part 1

Descriptive statistics were used to characterize the sample. Mean inspiratory and expiratory air flows,  $V_T$ , and time were determined by computing the mean of the 3 recordings at each air flow. The mean normal respiratory sound intensity and mean number of crackles and wheezes per breathing phase were determined by computing the mean of the 3 recordings at all anatomic locations. One-way repeated-measures analysis of variance was used to analyze differences in breathing patterns and respiratory sounds across air flows. When a statistically significant difference was found, Bonferroni post hoc tests were

performed. Statistical analysis was completed with the estimation of effect sizes. The effect size was computed via partial eta-square, as it is the index more commonly reported for analysis of variance (Levine & Hullett, 2002). Partial eta-square was interpreted as small ( $\geq 0.01$ ), medium ( $\geq 0.06$ ), or large ( $\geq 0.14$ ) effect (Cohen, 1969).

As recommended for intra-subject reliability (Rankin & Stokes, 1998), both relative (intraclass correlation coefficient [ICC]) and absolute reliability (Bland-Altman method) were used. The ICC equation (1, k) was used, where k=3 because 3 recordings were performed for each air flow. ICC was interpreted as excellent (> 0.75), moderate to good (0.4-0.75), or poor (< 0.4) (Fleiss, 1986). Bland-Altman method assesses the agreement between 2 sets of measures (Bland & Altman, 1986). Thus, random numbers were generated in MATLAB to delete one recording. Bland-Altman plots were created to analyze the distribution of results (Prism 5.01, GraphPad Software, La Jolla, California) (Bland & Altman, 1986).

Sample size was determined as described by Bonett (2002). A sample size of 13 subjects was required to estimate an ICC of 0.9 with a 95% CI width of 0.2 ( $\alpha$ =.05 and k=3) (Bonett, 2002).

## Part 2

Descriptive statistics were used to characterize the sample. The mean normal respiratory sound intensity, mean number of crackles and wheezes per breathing phase were determined by computing the mean of the 3 recordings for each anatomic location (trachea and right and left anterior, lateral, and posterior chest). The inter-subject variability in respiratory sound parameters was measured with the coefficient of variation, as it is useful for analyzing the variability of measures independently of the magnitude of the data (Lovie, 2005). It is defined as the SD divided by the mean (Abdi, 2010). The relative and absolute intra-subject reliability of respiratory sound parameters were computed, as described above, per anatomic location. Sample size for the coefficient of variation was estimated using the approach of Kelley (Kelley, 2007). Using data from part 1, we found that the coefficient of variation of normal respiratory sound intensity was between 0.17 and 0.25. We determined that a minimum of 59 individuals were needed for a coefficient of variation of 0.25 with a 95% CI width of 0.1 ( $\alpha$ =.05) (Kelley, 2007).

## Results

## Part 1

Thirteen subjects (10 males) were enrolled. Four subjects had mild air-flow limitation, 6 had moderate, and 3 had severe-to-very-severe air-flow limitation. All subjects used long-acting bronchodilators. Table 1 lists subjects' characteristics.

## Respiratory sounds

The intensity of normal respiratory sounds during inspiration and expiration was higher at an air flow of 0.7-1 L/s (post hoc p<.001) (Table 2). No significant differences were seen in the mean number of crackles (inspiratory, p=.45; expiratory, p=.066) and wheezes (inspiratory, p=.30; expiratory, p=.12). The relative reliability of normal respiratory sound intensity was moderate to excellent at the 3 air flows (see Table 2). Bland-Altman plots indicated greater agreement for normal respiratory sound intensity at an air flow of 0.4-0.6 L/s (Figs. 1B and 2B). The relative reliability of the mean number of inspiratory and expiratory crackles was found to be moderate to excellent for the 3 air flows (see Table 2). However, a higher level of agreement existed at an air flow of 0.4-0.6 L/s, with narrower limits of agreement (Figs. 1E and 2E). The relative reliability of mean number of inspiratory and expiratory wheezes was excellent at all air flows (see Table 2), although greater agreement was found at target air flows (Figs. 1H and 1I and 2H and 2I).

Characteristic	Values
Age, mean ± SD y	69.3 ± 8.6
Males/females, n	10/3
Current smokers, n	0
mMRC scale, median (IQR)	1 (1-2)
BMI, mean ± SD kg/m <sup>2</sup>	$29.5 \pm 3.4$
Exacerbations in past 3 m, n	
0	5
1	6
≥2	2
FEV1, mean ± SD L	$1.8 \pm 0.6$
$FEV_1$ , mean ± SD % predicted	70.9 ± 21.4
FEV <sub>1</sub> /FVC, mean ± SD	$0.66 \pm 0.09$
GOLD air-flow limitation, n	
Mild	4
Moderate	6
Severe to very severe	3
GOLD combined assessment, n	
A: low risk, less symptoms	3
B: low risk, more symptoms	7
C: high risk, less symptoms	1
D: high risk, more symptoms	2
N = 13. mMRC = modified Medical Research Council IQR = interquartile range BMI = body mass index GOLD = Global Initiative for Chronic Obstructive Lun-	_ q Disease

Table 1. Sociodemographic, anthropometric, and clinical characteristics of subjects

	Spontan	eous Air Flow	Air Flow	of 0.4-0.6 L/s	Air Flov	v of 0.7-1 L/s		
Characteristic	(mean ± SD)	ICC (95% CI)	(mean ± SD)	ICC (95% CI)	(mean ± SD)	ICC (95% CI)	p	Partial Eta-Square
Inspiratory normal respiratory	11.8 ± 2.16	0.74 (0.35-0.91)	11.32 ± 1.88	0.88 (0.7-0.96)	12.98 ±2.33	0.89 (0.73-0.96)	< .001	0.634
sound intensity, dB								
Expiratory normal respiratory	10.49 ± 2.05	0.66 (0.14-0.89)	10.30 ± 1.82	0.65 (0.13-0.88)	12.06 ± 2.96	0.74 (0.36-0.91)	< .001	0.757
sound intensity, dB								
Crackles on inspiration	1.57 ± 0.78	0.75 (0.38-0.92)	1.30 ± 0.60	0.71 (0.27-0.90)	1.38 ± 0.50	0.81 (0.52-0.94)	.45	0.064
Crackles on expiration	2.49 ± 1.35	0.78 (0.44-0.93)	1.47 ± 1.05	0.89 (0.74-0.97)	$1.34 \pm 0.64$	0.75 (0.39-0.92)	.066	0.203
Wheezes on inspiration	0.35 ± 0.49	0.79 (0.46-0.93)	0.31 ± 0.55	0.78 (0.46-0.93)	0.25 ± 0.31	0.75 (0.37-0.92)	.30	0.096
Mean number of wheezes on	0.59 ± 0.91	0.89 (0.72-0.96)	0.72 ± 1.72	0.99 (0.96-0.99)	$0.30 \pm 0.39$	0.78 (0.46-0.93)	.12	0.161
expiration								
Inspiratory flow, /s	0.38 ± 0.18	0.73 (0.32-0.91)	0.44 ± 0.14	0.95 (0.88-0.98)	0.7 ± 0.11	0.74 (0.34-0.91)	< .001	0.648
Expiratory flow, L/s	0.30 ± 0.17	0.88 (0.70-0.96)	$0.33 \pm 0.09$	0.92 (0.81-0.97)	$0.60 \pm 0.09$	0.77 (0.42-0.92)	< .001	0.751
Inspiratory VT, L	0.54 ± 0.18	0.76 (0.37-0.93)	0.57 ± 0.1	0.85 (0.63-0.95)	$0.96 \pm 0.22$	0.84 (0.61-0.95)	.001	0.431
Expiratory VT, L	0.56 ± 0.25	0.60 (0.01-0.87)	0.56 ± 0.11	0.73 (0.31-0.91)	$0.95 \pm 0.24$	0.70 (0.25-0.90)	.001	0.525
T <sub>I</sub> , s	1.36 ± 0.41	0.64 (0.02-0.89)	1.15 ± 0.28	0.85 (0.60-0.96)	1.24 ± 0.34	0.84 (0.59-0.95)	.60	0.097
T <sub>E</sub> , s	1.81 ± 0.53	0.72 (0.29-0.91)	1.71 ± 0.85	0.80 (0.50-0.93)	$1.50 \pm 0.40$	0.77 (0.42-0.92)	.21	0.123
N = 13. ICC = intraclass correlation coefficient $V_T$ = tidal volume $T_I$ = inspiratory time $T_E$ = expiratory time								

Table 2. Descriptive characteristics and intra-subject relative reliability of respiratory sounds and breathing pattern parameters at 3 air flows



Figure 1. Bland-Altman plots of inspiratory normal respiratory sound (NRS) intensity and mean number of crackles and wheezes between 2 recordings at 3 distinct air flows: spontaneous, 0.4-0.6 L/s, and 0.7-1 L/s. The solid lines represent the mean difference, and the dashed lines show the 95% limits of agreement.



Figure 2. Bland-Altman plots of expiratory normal respiratory sound intensity and mean number of crackles and wheezes between 2 recordings at 3 distinct air flows: spontaneous, 0.4-0.6 L/s, and 0.7-1 L/s. The solid lines represent the mean difference, and the dashed lines show the 95% limits of agreement.

## **Breathing pattern**

At an air flow of 0.7-1 L/s, significant higher flows (post hoc p<.001) and  $V_T$  (post hoc p<.05) were found (see Table 2). Inspiratory and expiratory times were similar across air flows (p=.6 and p=0.21, respectively). Intra-subject relative reliability of air flow,  $V_T$ , and time were higher at target air flow of 0.4-0.6 L/s (ICC of 0.73-0.95) compared with spontaneous air flow (ICC of 0.60-0.88) or a target air flow of 0.7-1 L/s (ICC of 0.70-0.84) (see Table 2). Figures 3 and 4 show that intra-subject absolute reliability was higher at 0.4-0.6 L/s. From the analysis of respiratory sound and breathing pattern parameters, it was verified that intra-subject reliability was higher at an air flow of 0.4-0.6 L/s.



Figure 3. Bland-Altman plots of inspiratory air flow, volume, and time between 2 recordings at 3 distinct air flows: spontaneous, 0.4-0.6 L/s, and 0.7-1 L/s. The solid lines represent the mean difference, and the dashed lines show the 95% limits of agreement.  $V_T$  = tidal volume;  $T_I$  = inspiratory time.



Figure 4. Bland-Altman plots of expiratory air flow, volume, and time between 2 recordings at 3 distinct air flows: spontaneous, 0.4-0.6 L/s, and 0.7-1 L/s. The solid lines represent the mean difference, and the dashed lines show the 95% limits of agreement.  $V_T$  = tidal volume;  $T_E$  = expiratory time.

Part 2

A total of 63 subjects (48 males) were enrolled. Most participants had low risk of exacerbations (A, 34.9%; B, 36.5%), and all used long-acting bronchodilators. Table 3 provides subjects' detailed characteristics.

Characteristic	Values
Age, mean ± SD y	$67.3 \pm 10.4$
Males/females, n	48/15
Current smokers, n (%)	16 (25.4)
mMRC scale, median (IQR)	1 (1-2)
BMI, mean ± SD kg/m <sup>2</sup>	29 ± 5
Exacerbations in past 3 m, n (%)	
0	35 (55.6)
1	17 (27)
≥ 2	11 (17.4)
FEV1, mean ± SD L	$1.9 \pm 0.6$
FEV <sub>1</sub> , mean ± SD % predicted	75.4 ± 22.9
FEV <sub>1</sub> /FVC, mean ± SD	$0.65 \pm 0.09$
GOLD air-flow limitation, n (%)	
Mild	35 (55.6)
Moderate	22 (34.9)
Severe to very severe	6 (9.5)
GOLD combined assessment, n (%)	
A: low risk, less symptoms	22 (34.9)
B: low risk, more symptoms	23 (36.5)
C: high risk, less symptoms	8 (12.7)
D: high risk, more symptoms	10 (15.9)
N = 63. mMRC = modified Medical Research Council IQR = interquartile range BMI = body mass index	

Table 3. Sociodemographic, anthropometric, and clinical characteristics of subjects

GOLD = Global Initiative for Chronic Obstructive Lung Disease.

## Respiratory sounds

Descriptive characteristics of normal respiratory sound intensity (from 9.41 to 14.71 dB), mean number of crackles (from 1.43 to 3.46), and mean number of wheezes (from 0.06 to 0.40) across locations are presented in table 4. Intersubject variability was high for all respiratory sound parameters; however, the mean number of crackles (coefficient of variation of 0.55-0.92) and wheezes (coefficient of variation of 1.15-2.22) presented the highest variation. Inter-subject variability was generally higher during expiration than inspiration for all respiratory sound parameters (normal respiratory sound intensity of 0.12-0.23 vs 0.15-0.21, mean number of crackles of 0.56-0.92 vs 0.55-0.78, mean number of wheezes of 1.36-2.22 vs.1.2-2.17) at most locations, with the exception of the trachea.

Normal respiratory sound intensity had an excellent relative and absolute reliability at all anatomic locations (see Table 4). The relative and absolute reliability of the mean number of crackles and wheezes were moderate to excellent at all anatomic locations. The only exceptions were the mean number of inspiratory and expiratory crackles at the trachea, which showed poor relative and absolute reliability.

Table 4. Descriptive characteristics, inter-subject variability, and relative and absolute reliability of respiratory sounds per anatomic location at an air flow of 0.4-0.6 L/s

Characteristic and	Maar OD	Coefficient of		Mean	95% Limits of
Anatomic Location	Mean ± SD	Variation	100 (95%01)	Difference ± SD	Agreement
Inspiratory normal respiratory					
sound intensity, dB					
Trachea	12.94 ± 3.67	0.28	0.95 (0.92-0.97)	-0.28 ± 1.22	-2.68 to 2.12
Anterior right chest	12.43 ± 2.00	0.16	0.90 (0.85-0.94)	0.18 ± 0.91	-1.62 to 1.97
Anterior left chest	10.43 ± 1.59	0.15	0.93 (0.89-0.95)	-0.12 ± 0.99	-2.07 to 1.83
Lateral right chest	12.88 ± 2.73	0.21	0.93 (0.89-0.96)	0.28 ± 1.48	-2.61 to 3.18
Lateral left chest	13.65 ± 2.83	0.21	0.88 (0.82-0.92)	0.02 ± 1.69	-3.30 to 3.33
Posterior right chest	14.71 ± 2.88	0.20	0.93 (0.89-0.96)	0.16 ± 0.89	-1.58 to 1.91
Posterior left chest	12.02 ± 2.25	0.19	0.93 (0.89-0.96)	0.22 ± 1.34	-2.40 to 2.84
Expiratory normal respiratory					
sound intensity, dB					
Trachea	13.20 ± 3.33	0.25	0.93 (0.89-0.95)	-0.26 ± 1.47	-3.14 to 2.62
Anterior right chest	11.16 ± 1.36	0.12	0.88 (0.81-0.92)	0.13 ± 0.92	-1.68 to 1.94
Anterior left chest	9.41 ± 1.20	0.13	0.91 (0.86-0.94)	-0.08 ± 0.80	-1.65 to 1.49
Lateral right chest	11.68 ± 2.42	0.21	0.94 (0.90-0.96)	-0.07 ± 1.63	-3.26 to 3.11
Lateral left chest	12.58 ± 2.90	0.23	0.88 (0.81-0.92)	-0.38 ± 1.63	-3.58 to 2.81
Posterior right chest	12.96 ± 2.83	0.22	0.89 (0.83-0.93)	0.14 ± 0.95	-1.73 to 2.00
Posterior left chest	10.69 ± 2.01	0.19	0.87 (0.81-0.92)	0.19 ± 1.66	-3.06 to 3.44
No. of crackles on inspiration					
Trachea	1.45 ± 0.90	0.62	-0.34 (-1.19-0.22)	-1.83 ± 1.57	-4.91 to 1.25
Anterior right chest	2.07 ± 1.15	0.55	0.79(0.69-0.87)	0.05 ± 1.17	-2.24 to 2.34
Anterior left chest	$1.43 \pm 0.80$	0.56	0.55(0.32-0.72)	0.15 ± 0.98	-1.77 to 2.06
Lateral right chest	2.57 ± 1.61	0.63	0.59(0.37-0.74)	0.23 ± 1.72	-3.14 to 3.60
Lateral left chest	2.24 ± 1.75	0.78	0.73(0.59-0.83)	-0.10 ± 1.36	-2.77 to 2.56
Posterior right chest	2.86 ± 1.75	0.61	0.77(0.65-0.86)	0.31 ± 1.54	-2.70 to 3.33
Posterior left chest	2.37 ± 1.77	0.74	0.42(0.08-0.65)	1.45 ± 1.27	-1.03 to 3.93
No. of crackles on expiration					
Trachea	1.65 ± 1.11	0.68	0.02 (-0.61-0.43)	-1.75 ± 1.95	-5.57 to 2.08
Anterior right chest	3.07 ± 1.72	0.56	0.78 (0.67-0.86)	0.22 ± 1.47	-2.67 to 3.10
Anterior left chest	2.15 ± 1.57	0.73	0.90 (0.85-0.94)	0.25± 1.22	-2.14 to 2.64
Lateral right chest	3.33 ± 2.30	0.69	0.52 (0.27-0.7)	-0.38 ± 2.18	-4.65 to 3.89
Lateral left chest	$2.89 \pm 2.06$	0.71	0.64 (0.45-0.77)	-0.13 ± 1.28	-2.64 to 2.38

Posterior right chest	$3.46 \pm 2.80$	0.81	0.86 (0.79-0.91)	0.23 ± 1.70	-3.10 to 3.56
Posterior left chest	2.99 ± 2.74	0.92	0.57 (0.31-0.74)	1.31 ± 1.24	-1.12 to 3.74
No. of wheezes on inspiration					
Trachea	$0.35 \pm 0.47$	1.34	0.61 (0.41-0.75)	$0.20 \pm 0.63$	-1.04 to 1.44
Anterior right chest	$0.16 \pm 0.34$	2.17	0.87 (0.81-0.92)	$0.00 \pm 0.18$	-0.36 to 0.35
Anterior left chest	0.06± 0.11	1.68	0.44 (0.15-0.64)	$0.05 \pm 0.20$	-0.33 to 0.43
Lateral right chest	$0.20 \pm 0.30$	1.51	0.49 (0.23-0.68)	-0.01 ± 0.32	-0.64 to 0.61
Lateral left chest	0.16 ± 0.20	1.20	0.42 (0.12-0.63)	0.05 ± 0.38)	-0.70 to 0.80
Posterior right chest	$0.18 \pm 0.30$	1.65	0.80 (0.70-0.88)	-0.19 ± 0.38	-0.92 to 0.55
Posterior left chest	0.21 ± 0.27	1.27	0.35 (0.02-0.59)	0.01 ± 0.30	-0.57 to 0.59
No. of wheezes on expiration					
Trachea	$0.37 \pm 0.42$	1.15	0.63 (0.43-0.76)	$0.14 \pm 0.55$	-0.94 to 1.23
Anterior right chest	$0.22 \pm 0.40$	1.82	0.84 (0.75-0.9)	$0.03 \pm 0.25$	-0.47 to 0.53
Anterior left chest	0.13 ± 0.28	2.22	0.83 (0.74-0.89)	0.04 ± 0.31	-0.57 to 0.66
Lateral right chest	$0.40 \pm 0.70$	1.75	0.67 (0.49-0.79)	$0.06 \pm 0.38$	-0.69 to 0.81
Lateral left chest	$0.36 \pm 0.54$	1.48	0.64 (0.46-0.77)	$0.02 \pm 0.46$	-0.88 to 0.93
Posterior right chest	$0.28 \pm 0.39$	1.36	0.65 (0.47-0.7)	-0.08 ± 0.42	-0.90 to 0.73
Posterior left chest	$0.31 \pm 0.53$	1.70	0.77 (0.65-0.85)	0.12 ± 0.31	-0.49 to 0.74
N = 63.	•				

ICC = intraclass correlation coefficient

#### Discussion

To the best of our knowledge, this is the first study investigating intersubject variability and intra-subject reliability of respiratory sounds at distinct air flows and anatomic locations in subjects with stable COPD. The main findings indicated that respiratory sound parameters are (1) more reliable at an air flow of 0.4-0.6 L/s, (2) highly variable across subjects, and (3) reliable overall at all standardized anatomic locations.

The normal respiratory sound intensity increased at higher air flows. The link between sound intensity and air flow has long been recognized (Ploysongsang, Pare, & Macklem, 1982). From spontaneous to target air flows, the mean number of inspiratory and expiratory crackles had a tendency to decrease. This has also been observed in subjects with interstitial pulmonary fibrosis when comparing crackle rate during normal and deep-breathing maneuvers (Vyshedskiy, Ishikawa, & Murphy, 2011). This may be related to the effect of lung expansion, as recordings were repeated at short intervals (Piirila & Sovijarvi, 1995). During the first breathing maneuvers, regions of deflated airways

probably opened, and in the following maneuvers, the production of crackles decreased (Piirila & Sovijarvi, 1995). The mean number of wheezes had also a tendency to decrease. The consecutive expirations at increased air flows could have been sufficient to decrease the cross-sectional diameter of airways (particularly of the second generation of the airway tree) (Bohadana et al., 2014), increase linear velocities, and aid secretion movement (Pavia, Agnew, Lopez-Vidriero, & Clarke, 1987). This phenomenon could have reduced the narrowing airway and thus the production of wheezes (Bohadana et al., 2014; Meslier, Charbonneau, & Racineux, 1995). These findings show that the characteristics of respiratory sounds are variable at distinct air flows, reinforcing the need to use standardized air flows during computerized auscultation. This will be essential if respiratory sounds are to become a clinical marker to evaluate the effectiveness of treatments.

The relative reliability of normal respiratory sound intensity and of the mean number of crackles was moderate to excellent at the 3 air flows. However, ICCs in isolation do not provide a true picture of reliability (Rankin & Stokes, 1998). The Bland-Altman method is independent of the true variability and provide detail regarding the nature of the observed intra-subject variability (Rankin & Stokes, 1998). The agreement assessed from Bland-Altman method was found to be acceptable for normal respiratory sound intensity and mean number of crackles at the 3 air flows. Nevertheless, for these respiratory sound parameters, a higher agreement was found at an air flow of 0.4-0.6 L/s. The reliability of the mean number of wheezes was excellent for all air flows. Forced expiratory wheezes have also been found to be reproducible in healthy subjects (Beck & Gavriely, 1990). No systematic bias was observed at any tested air flow, although a higher agreement was found at target air flows.

Regarding breathing pattern, the mean inspiratory (0.38  $\pm$  0.18 L/s) and expiratory (0.3  $\pm$  0.17 L/s) flows at spontaneous air flow were similar to values reported previously (Dal Negro, Turati, Micheletto, & Menegoni, 2012; Diaz et al., 2000; Diaz et al., 2001). Significantly higher V<sub>T</sub> was observed at air flow of 0.7-1

L/s, which was expected due to the direct relationship between air flow and volume (Schlegelmilch & Kramme, 2011). Inspiratory (1.15-1.36 s) and expiratory (1.50-1.81 s) times were within commonly reported values in the literature (Hill et al., 2007). In subjects with COPD, the breathing pattern has also been found to be similar during constant and incremental loaded breathing tests (Hill et al., 2007). The intra-subject reliability of breathing pattern parameters was found to be better at target air flows (Vlemincx, Diest, & Bergh, 2012). This might be due to the explicit instructions to breathe at a typical peak air flow, which further reduced the breathing complexity (Dames et al., 2014). In accordance to this, breathing pattern was also more reliable at target flows, especially at an air flow of 0.4-0.6 L/s. This is probably explained by the fact that an air flow of 0.7-1 L/s was the most demanding for subjects to perform and maintain during the 20-s recordings (Vlemincx et al., 2012). Therefore, from analysis of respiratory sound and breathing pattern parameters, it can be concluded that a target airflow of 0.4-0.6 L/s is the most reliable for characterizing normal respiratory sounds, crackles, and wheezes in subjects with COPD.

At an air flow of 0.4-0.6 L/s, the normal respiratory sound intensity across locations was found to be 9.41-14.71 dB. These values are slightly lower than those found for healthy subjects at the right posterior chest (inspiration of 17.17 dB, expiration of 11.50 dB) (Pasterkamp & Sanchez, 1996). Nevertheless, in this previous study, healthy subjects breathed at a higher target flow ( $1.5 \pm 0.2$  L/s) (Pasterkamp & Sanchez, 1996). The mean number of crackles was 1.43-3.46, within the previously described range (0.73 - 5) (Murphy, 2008; Piirila, Sovijarvi, Kaisla, Rajala, & Katila, 1991). Wheezes were not frequent across locations (from 0.06 to 0.40), which is in line with a previous study (Murphy, 2008).

Nevertheless, even when recorded with the most reliable air flow, respiratory sound parameters exhibited considerable inter-subject variability. Among other factors, differences regarding demographic, anthropometric and clinical (eg, dyspnea, COPD severity, and history of exacerbations) characteristics might have contributed to this variability across subjects. High inter-subject variability of respiratory sounds has also been reported previously in subjects with cystic fibrosis and bronchiectasis (Marques, Bruton, & Barney, 2009). However, this inter-subject variability is similar to other biosignals that support clinical decisions (eg, heart rate variability, electromyography) (Lapatki, Stegeman, & Jonas, 2003; Stockhorst, Huenig, Ziegler, & Scherbaum, 2011). From a clinical perspective, this inter-subject variability limits inferences at the group level, as respiratory sound patterns may fail to represent patterns seen in individuals. For example, increased wheezing has been recognized as one of the signs of a COPD exacerbation (Sapey & Stockley, 2006). Nevertheless, due to the high variability of this respiratory sound parameter, a small increase in the mean number of wheezes may indicate a change in the clinical status for one patient, but not to another. This highlights the importance of supporting healthcare professionals in clinical decisions in the interpretation of respiratory sound changes at an individual level and in combination with other clinical data.

Normal respiratory sound intensity and mean number of crackles and wheezes were found to be reliable across all anatomic locations. At the trachea, however, the mean number of crackles had poor reliability. This result may be due to low generation of this adventitious sound in this region of the respiratory tract. It has been generally accepted that crackles are generated when an airway opens during inspiration or closes during expiration (Piirila & Sovijarvi, 1995; Vyshedskiy et al., 2009). Because the trachea is characterized by a large diameter and rigid wall, it is unlikely to open or collapse during tidal breathing.

In addition, normal respiratory sound intensity had lower variability and higher reliability than mean number of crackles and wheezes at all anatomic locations. Normal respiratory sounds are produced when breathing and can be heard both during inspiration and expiration (nearly silent) (Sovijärvi et al., 2000). Crackles and wheezes are superimposed events on normal respiratory sounds (Sovijärvi et al., 2000), and timing may not be perfectly repeatable from breath to breath. Health professionals may thus more confidently rely on changes in normal respiratory sound intensity than mean number of adventitious respiratory sounds. Study limitations

The recording of distinct air flows in the same session and at relatively short intervals may have influenced the results. However, to minimize bias, the order of tests was standardized, and subjects were instructed to rest as needed. Future studies assessing intra-subject reliability could perform the recordings in different sessions within the same day. It would be also interesting in future studies to explore the intra-subject test-retest reliability of respiratory sounds to understand their stability and reliability over time. The present study focused on only one parameter per respiratory sound. Future studies could investigate the reliability of respiratory sounds using other parameters that also have clinical relevance (Marques, Oliveira, & Jácome, 2014). Additionally, the unbalanced sample in terms of COPD severity is another limitation of the present study. The samples were composed mainly of subjects with mild and moderate air-flow limitation, and thus, it was not possible to explore how the disease severity related to the variability/reliability of respiratory sound parameters. However, as the breathing pattern at an airflow of 0.4-0.6 L/s is similar to that in subjects with advanced COPD (Hill et al., 2007) and air-flow variability is not related with COPD severity (Dames et al., 2014), the disease severity might not play a significant role. Future studies should investigate this, however.

# Conclusions

The main findings suggest that respiratory sound parameters are more reliable at an air flow of 0.4-0.6 L/s, highly variable across subjects with COPD, and reliable overall at all standardized anatomic locations. In the future, respiratory sounds should be assessed in subjects with COPD using this target air flow and these anatomic locations. More studies are needed to draw definite conclusions on air flow standards for recording respiratory sounds in subjects with COPD and other respiratory diseases.

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Study IV

Computerized respiratory sounds: a comparison between patients with stable and exacerbated COPD

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#### Abstract

**Introduction:** Diagnosis of acute exacerbations of chronic obstructive pulmonary disease (AECOPD) is often challenging as it relies on patients' clinical presentation. Computerized respiratory sounds (CRS), namely crackles and wheezes, may have the potential to contribute for the objective diagnosis/monitoring of an AECOPD.

**Objectives:** This study explored if CRS differ during stable and exacerbation periods in patients with COPD.

**Methods:** 13 patients with stable COPD and 14 with AECOPD were enrolled. CRS were recorded simultaneously at trachea, anterior, lateral and posterior chest locations using seven stethoscopes. Airflow (0.4-0.6 L/s) was recorded with a pneumotachograph. Breathing phases were detected using airflow signals; crackles and wheezes with validated algorithms.

**Results:** At trachea, anterior and lateral chest, no significant differences were found between the two groups in the number of inspiratory/expiratory crackles or inspiratory wheeze occupation rate. At posterior chest, the number of crackles (median 2.97-3.17 vs. 0.83-1.2, p<0.001) and wheeze occupation rate (median 3.28%-3.8% vs. 1.12%-1.77%, p=0.014-0.016) during both inspiration and expiration were significantly higher in patients with AECOPD than in stable patients. During expiration, wheeze occupation rate was also significantly higher in patients with AECOPD at trachea (median 3.12% vs. 0.79%, p<0.001) and anterior chest (median 3.55% vs. 1.28%, p<0.001).

**Conclusion:** Crackles and wheezes are more frequent in patients with AECOPD than in stable patients, particularly at posterior chest. These findings suggest that these CRS can contribute to the objective diagnosis/monitoring of AECOPD, which is especially valuable considering that they can be obtained by integrating computerized techniques with pulmonary auscultation, a non-invasive method that is a component of patients' physical examination.

## Introduction

Acute exacerbations constitute one of the most important causes of morbidity and mortality in patients with chronic obstructive pulmonary disease (COPD) and account for the greatest proportion of the disease burden on health care systems (Perera, Armstrong, Sherrill, & Skrepnek, 2012). Therefore, methods for prevention and early diagnosis of acute exacerbations of COPD (AECOPD) are of paramount importance worldwide (Criner et al., 2015).

According to the Global Initiative for Chronic Obstructive Lung Diseases (GOLD), diagnosis of an AECOPD relies on the clinical presentation of the patient complaining of an acute change of symptoms, that is beyond normal day-to-day variation (Vestbo et al., 2013). This may affect patients' diagnosis and optimal management and ultimately increase the severity of the exacerbation, length of hospitalization and health costs.

During exacerbations, there is increased hyperinflation and gas trapping, with reduced expiratory flow, thus accounting for the increased dyspnea (Parker, Voduc, Aaron, Webb, & O'Donnell, 2005). Respiratory sounds (RS), namely crackles and wheezes, are directly related to movement of air, changes within lung morphology and presence of secretions (Bohadana, Izbicki, & Kraman, 2014; Kiyokawa & Pasterkamp, 2002). Moreover, in a recent study, it was possible to characterize AECOPD into two phenotypes based on computerized RS analysis (Sánchez Morillo, Astorga Moreno, Fernández Granero, & León Jiménez, 2013).

From the available evidence, it appears that computerized RS provide valuable information regarding the respiratory system and may have the potential to contribute for the objective diagnosis and monitoring of an AECOPD. However, to date, no studies exist exploring if computerized RS differ significantly between stable and exacerbation periods in COPD.

Thus, this study explored differences in computerized RS between patients with stable COPD and patients with AECOPD.

## Materials and Methods

#### Study design and participants

A cross-sectional study with 15 outpatients with stable COPD, recruited from one primary care center, and 15 outpatients with AECOPD, recruited from one emergency department of a general hospital, was conducted between January and October 2013. Patients were included if they had a diagnosis of COPD according to the GOLD (Vestbo et al., 2013). Patients with regular appointments with their general practitioner and clinically stable for 1 month prior to the study (no hospital admissions, exacerbations or changes in medication for the respiratory system) were eligible for the group of stable COPD. Diagnosis of an AECOPD according to the GOLD (Vestbo et al., 2013), and clinical presentation compatible with mild to moderate AECOPD (no need for hospital admission) (Rodriguez-Roisin, 2000) were inclusion criteria for the group of patients with AECOPD. Exclusion criteria for both groups were presence of coexisting respiratory diseases or severe neurological, musculoskeletal or psychiatric impairments. Approval for this study was obtained from the ethics committees. Eligible patients were identified via clinicians and were then contacted by researchers, who explained the purpose of the study. When patients agreed to participate, an appointment with the researchers was scheduled in a room at the University of Aveiro. In patients with AECOPD, this appointment was scheduled within 24-48 h of hospital presentation. Written informed consent was obtained prior to any data collection.

#### Data collection procedures

Sociodemographic (age, gender) and clinical (body mass index and medication) data were first recorded. Dyspnea was assessed with the modified British Medical Research Council questionnaire (Vestbo et al., 2013). The questionnaire comprises five grades in a scale from 0 to 4, with higher grades indicating greater perceived dyspnea. Then, RS and lung function were collected. Severity of COPD was collected from patients' records. All assessments were performed by two physiotherapists in a standardized order.

Airflow and RS were acquired simultaneously for 20 s (Vyshedskiy & Murphy, 2012). Patients were in a seated-upright position, wearing a nose clip and breathing through a mouthpiece at a typical tidal airflow (0.4-0.6 L/s)(Fiz, Kraman. Wodicka, & Pasterkamp, 2008) Gnitecki, into а heated pneumotachograph (3830, Hans Rudolph, Inc., Shawnee, KS, USA). RS were shown to be reliable at this selected airflow (Jácome & Marques, 2015a). Visual biofeedback of the flow signal was presented to patients (RSS 100R Research Pneumotach System, Hans Rudolph, Shawnee, KS, USA) to standardize the airflow during recordings.

RS recordings followed computerized respiratory sound analysis (CORSA) guidelines for short-term acquisitions (Rossi et al., 2000). Data were acquired simultaneously at seven chest locations (trachea; right and left: anterior, lateral and posterior)(Rossi et al., 2000) using the LungSounds@UA interface (Pinho, Oliveira, Oliveira, Dinis, & Marques, 2014). Seven chest pieces (Classic II S.E., Littmann®, 3M, St. Paul, MN, USA), with a microphone (flat response between 20Hz and 19kHz - TOM-1545P-R, Projects Unlimited, Inc.®, Dayton, OH, USA) and preamplifier circuit (Intelligent Sensing Anywhere®, Coimbra, PT) in the main tube, were attached to the patient's skin with adhesive tape (Soft Cloth Surgical Tape, 3M, St. Paul, MN, USA). The resulting analogue sound signals were further amplified and converted to digital by a multi-channel audio interface (M-Audio® ProFire 2626, Irwindale, CA, USA). The signal was converted with a 24-bit resolution at a sampling rate of 44.1 KHz and recorded in wav. format.

A spirometric test (MicroLab 3500, CareFusion, Kent, UK) was last performed according to standardized guidelines (Miller et al., 2005).

## Signal processing

All files were processed using algorithms written in Matlab®R2009a (Mathworks, Natick, MA, USA). Breathing phases were automatically detected using the flow signals. Signals were timed synchronized to combine the detected breathing phases with sound signals.

Crackles are adventitious, discontinuous and explosive sounds that can be classified as fine or coarse (Sovijärvi et al., 2000). Fine crackles are high pitch, low amplitude and short duration (two cycle duration <10 ms), while coarse crackles are low pitch, high amplitude and long duration (two cycle duration >10 ms)(Sovijärvi et al., 2000). As CORSA guidelines do not endorse a specific method to detect crackles, a multi-algorithm agreement method was used (Hadjileontiadis & Rekanos, 2003; Lu & Bahoura, 2008; Vannuccini, Rossi, & Pasquali, 1998). This multi-algorithm technique was based on the implementation of established algorithms, i.e., (i) the time-domain waveform identification approach of Vannuccini, Rossi et al. (1998), (ii) the fractal dimension filtering technique of Hadjileontiadis and Rekanos (2003), and (iii) the fractal dimension filtering technique with variations inspired in the work of Lu and Bahoura (2008). This multi-algorithm technique was found to have high sensitivity (91.4%) and precision (83.7%) and a 7% improvement over the performance of the individual algorithms (Quintas, Campos, & Marques, 2013). The total number of crackles, as well as the number of coarse and fine crackles, were extracted per breathing phase (Sovijärvi et al., 2000).

Wheezes are adventitious, continuous (≥100 ms) sounds with a musical character (dominant frequency usually over 100 Hz) (Sovijärvi et al., 2000). Wheezes were classified as monophonic, when containing essentially a single frequency, or as polyphonic, when containing several frequencies (Sovijärvi et al., 2000). Wheezes were detected using an algorithm based on time-frequency analysis, which was found to have high sensitivity (95.5%) and specificity (93.7%) (Taplidou & Hadjileontiadis, 2007). In the implemented algorithm, the signal was digitally filtered (band pass 60–2100 Hz, order-8 Butterworth) and resampled (to 5512s-1) before the Short-time Fourier transform calculation (Taplidou & Hadjileontiadis, 2007). A smoothing procedure based on box filtering was also applied to remove noise from the signal. Peaks higher than a specific magnitude threshold were then selected and classified as wheezes or nonwheezes, according to a set of criteria that includes: local maxima, peak coexistence and continuity in time (Taplidou & Hadjileontiadis, 2007). The total wheeze occupation

rate, and the monophonic and polyphonic wheeze occupation rates were extracted per breathing phase (Sovijärvi et al., 2000).

#### Statistical analysis

A power calculation was not performed since the expected sample variance in crackle or wheeze parameters were unknown in stable and exacerbated patients with COPD. Descriptive statistics were used to describe the sample. Independent *t*-tests for continuous, Mann Whitney *U*-tests for ordinal and chi-square tests for categorical data were used to compare the sociodemographic and clinical characteristics between groups.

RS data were explored per each one of the seven recorded locations, however, no significant differences were found between right and left locations. To simplify the interpretability of the findings, data from right and left were pooled for each chest region. Median and interquartile range were used to describe RS parameters. Mann–Whitney *U*-tests were used to compare RS parameters between groups at trachea, anterior, lateral and posterior chest. When statistically significant differences were found for the number of crackles or wheeze occupation rate, a comparison of the type of crackles or wheezes was also performed.

Statistical analyzes were completed with the estimation of effect size. The r, interpreted as small ( $r \ge 0.2$ ), medium ( $r \ge 0.3$ ) or large ( $r \ge 0.5$ )(Cohen, 1988), was used as this is the effect size estimate recommended for Mann–Whitney *U*tests (Fritz, Morris, & Richler, 2012). Statistical analyzes were performed using IBM SPSS Statistics version 20.0 (IBM Corporation, Armonk, NY, USA) and plots created using GraphPad Prism version 5.01 (GraphPad Software, Inc., La Jolla, CA, USA). The level of significance was set at 0.05.

## Results

#### Participants

Of the 30 patients eligible, 2 declined to participate as they did not perceive the study as relevant and 1 failed to keep the appointment. Twenty-seven participants were enrolled, 13 with stable COPD and 14 with mild/moderate with long-acting AECOPD. participants medicated All were inhaled bronchodilators. Patients with AECOPD were additionally medicated with systemic corticosteroids and antibiotics. No significant differences were noted between groups, with the exception of perceived dyspnea (p=0.010; Table 1).

Characteristics	Stable	Acute exacerbation	р
	(n = 13)	(n = 14)	
Age (years), M ± SD	69 ± 9	67 ± 12	0.512
Sex (male), n	10	9	0.275
mMRC, M[IQR]	1 [1, 2]	2 [1, 3]	0.010
BMI (kg/m²), M ± SD	27 ± 4	25 ± 5	0.322
FEV1 (L), M ± SD	1.85 ± 0.61	1.47 ± 0.54	0.090
FEV <sub>1</sub> (% predicted(Quanjer et al., 1993)), M ± SD	71 ± 21	59 ± 20	0.799
FEV <sub>1</sub> /FVC (%), M ± SD	66 ± 9	56 ± 16	0.119
GOLD classification, n			
Mild	4	3	0.410
Moderate	6	7	
Severe-to-very-severe	3	4	

Table 1. Sociodemographic and clinical characteristics of participants

mMRC, modified British Medical Research Council questionnaire;

IQR, interquartile range; BMI, body mass index;

FEV<sub>1</sub>, forced expiratory volume in one second; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

## Computerized RS

### Crackles

Fig. 1 presents the number of crackles at each chest region in patients with stable and AECOPD. There were no significant differences between the two groups in number of inspiratory and expiratory crackles at trachea, anterior and lateral chest (Fig. 1). However, at posterior chest, patients with AECOPD had significantly more inspiratory (2.97[2.15-4.13] vs. 1.20[0.72-1.62], p<0.001, r=-

M, median;

0.701) and expiratory (3.17[2.73-4.05] vs. 0.83[0.53-1.55], p<0.001, r=-0.819) crackles than stable patients (Fig. 1). Fig. 2 shows a respiratory sound file at posterior chest from a stable and an exacerbated patient with COPD.



Figure 1. Number of crackles at trachea, anterior, lateral and posterior chest in patients with stable COPD and AECOPD. Data are presented as median and interquartile range. Significant differences are identified with \* (p<0.05).



Figure 2. Time amplitude plots of respiratory sounds recorded at posterior chest from (a) a patient with stable COPD and (b) a patient with acute exacerbation of COPD. A respiratory sound file of 20 s and a breathing cycle is represented for each patient, inspiration is represented by the line above zero, while expiration corresponds to the line below zero. Each black border indicates a crackle.
When analyzing differences regarding type of crackles at posterior chest (Fig. 3), coarse crackles were significantly more frequent in patients with AECOPD at inspiration (2.73[2.02-3.8] vs. 0.93[0.6-1.33], p<0.001, *r*=-0.736) and expiration (3.07[2.48-3.8] vs. 0.73[0.47-1.22], p<0.001, *r*=-0.827). Fine crackles were almost absent in both groups, with no significant differences between them (inspiration 0.2[0.07-0.4] vs. 0.2[0.07-0.28], p=0.638, *r*=-0.064; expiration 0.17[0.07-0.33] vs. 0.13[0.07-0.22], p=0.362, *r*=-0.124).



Figure 3. Number of coarse and fine crackles at posterior chest in patients with stable COPD and AECOPD. Data are presented as median and interquartile range. Significant differences are identified with \* (p<0.05).

#### Wheezes

During inspiration, wheeze occupation rate was found to be significantly different between groups only at posterior chest (3.28[1.02-7.31]% vs. 1.12[0.66-2.29]%, p=0.014, *r*=-0.333) (Fig. 4). During expiration, wheeze occupation rate was significantly higher in patients with AECOPD at the trachea (3.12[2.43-6.74]% vs. 0.79[0-1.99]%, p<0.001, *r*=-0.637), anterior (3.55[1.9-10.19]% vs. 1.28[0-4.18]%, p<0.001, *r*=-0.388) and posterior (3.80[2-10.24]% vs. 1.77[0.58-4.17]%, p=0.016, *r*=-330) chest (Fig. 4).



Figure 4. Wheeze occupation rate at trachea, anterior, lateral and posterior chest in patients with stable COPD and AECOPD. Data are presented as median and interquartile range. Significant differences are identified with \* (p<0.05).

Regarding wheeze type, significant differences between groups were only observed on monophonic wheeze occupation rate at trachea (expiration 2.94[1.88-5.71]% vs. 0.79[0-1.55]%; p<0.001; *r*=-0.646), anterior (expiration 3.43[1.9-9.49]% vs. 1.28[0-4.18]; p=0.004%; *r*=-0.386) and posterior (inspiration 15.98[5.12-28.41]% vs. 5.58[3.31-11.45]%, p=0.014, *r*=-0.333; expiration 3.80[1.77-8.76]% vs. 1.68[0.58-4]%, p=0.015, *r*=-0.332) chest (Fig. 5). Fig. 6 shows spectrograms of RS recorded at posterior chest from a stable and an exacerbated patient with COPD.



Figure 5. Monophonic and polyphonic wheeze occupation rate at trachea, anterior and posterior chest in patients with stable COPD and AECOPD. Data are presented as median and interquartile range. Significant differences are identified with \* (p<0.05).





# Discussion

The main findings indicated that crackles and wheezes are significantly more frequent in patients with AECOPD, especially at posterior chest.

It has been generally accepted that crackles are generated when an airway opens during inspiration or closes during expiration (Piirila & Sovijarvi, 1995; Vyshedskiy et al., 2009). In patients with stable COPD, a median of 1.20 inspiratory and of 0.83 expiratory crackles were found at posterior chest, which is slightly lower than the results of Piirila et al. (inspiratory 2.9; expiratory 0.73) (Piirila, Sovijarvi, Kaisla, Rajala, & Katila, 1991). Patients with AECOPD had significantly more inspiratory and expiratory crackles (2.97-3.17), with large effect sizes. This may be related to the excessive production of secretions in AECOPD (O'Donnell & Parker, 2006), which alter airway diameter and characteristics (Pasterkamp, Kraman, & Wodicka, 1997; Vyshedskiy, Ishikawa, & Murphy, 2011), possibly causing more sudden airway opening/closing events. Therefore, the occurrence of more coarse and fine crackles in patients with AECOPD than in stable patients was expected (Jácome & Marques, 2015b; Piirila et al., 1991). In fact, more crackles, especially fine, have been identified in lower respiratory tract infections (Murphy et al., 2004). However, in the present study, only more coarse crackles were observed and fine crackles were almost absent in both groups. This may be due to the use of stethoscopes to record RS, which tend to amplify low frequencies and attenuate high frequencies (Melbye, 2001; Pasterkamp et al., 1997). Future research should therefore focus in developing technologies to acquire RS with higher quality. The posterior chest was found to be the most informative. The posterior chest is a gravity-dependent region, where greater volume changes occur during inspiration (Pennati, Salito, Baroni, Woods, & Aliverti, 2014). As crackles genesis is related with critical transitions in the airway volume this chest region might be the most useful to assess and monitor patients with COPD (Nath & Capel, 1974; Vyshedskiy et al., 2009). Additionally, anterior and lateral regions are normally characterized by recordings with lower quality (Murphy et al., 2004), which may also have limited crackles' algorithm performance.

Inspiratory and expiratory wheeze occupation rates at the posterior chest were found to be around 1-2% in stable patients. A previous study from Murphy presented higher wheeze occupation rates (inspiratory 2% and expiratory 12%)(Murphy, 2008). These differences may be due to distinct procedures used to record and analyze RS. In the present study, RS were recorded with a standardized airflow, at seven locations and wheeze occupation rate was

computed for four chest regions (trachea, anterior, lateral and posterior chest). In Murphy's study, RS were recorded with an unstandardized airflow, at 16 locations and wheeze occupation rate was the average of all locations (Murphy, 2008). Inspiratory and expiratory wheeze occupation rates at posterior chest were significantly higher in patients with AECOPD (median differences 1.67 and 2.26), with medium effect sizes. At trachea and anterior chest, significant differences were also observed during expiration (median differences 2.6 and 2.12). Increased wheezing has long been described as a commonly observed sign of an AECOPD (Greene et al., 2011; Greenstone, 2010; Seemungal, Donaldson, Bhowmik, Jeffries, & Wedzicha, 2000). During exacerbation periods, the increased airway inflammation induces edema, bronchospasm and sputum production (O'Donnell & Parker, 2006). These airway changes will probably reduce the critical flutter velocity, producing oscillations of the airway walls more easily (Meslier, Charbonneau, & Racineux, 1995). The differences were only statistically significant for monophonic wheeze occupation rate. Polyphonic wheeze occupation rate tended to be higher in patients with AECOPD, which was anticipated as the presence of polyphonic wheezes indicates a more serious obstruction (Fiz et al., 2006).

Findings from the present study suggest that the detection of increased or decreased number of crackles and/or wheeze occupation rate may have the potential to contribute to the objective diagnosis and/or monitoring of AECOPD. This is in line with recent research stating that computerized RS can support the diagnosis of pneumonia and characterize acute exacerbations in patients with COPD (Sánchez Morillo, Astorga Moreno, et al., 2013; Sánchez Morillo, Leon Jimenez, & Moreno, 2013). Furthermore, the findings also indicate that, in the absence of time to perform a complete pulmonary auscultation, computerized auscultation of the posterior chest can provide the most relevant clinical information. Nevertheless, similar to other biosignals that support clinical decisions (e.g., heart rate variability, electromyography)(Lapatki, Stegeman, & Jonas, 2003; Stockhorst, Huenig, Ziegler, & Scherbaum, 2011), computerized RS have high intersubject variability(Jácome & Marques, 2015a), and thus, a change

in RS may indicate the onset of an AECOPD for one patient, but not for another. To overcome this limitation, it is fundamental to record computerized RS of each individual during routine appointments or via telemedicine applications. This would facilitate the definition of individual RS profiles and alert thresholds indicating the onset/recovery of acute exacerbations.

This study has a number of limitations that need to be acknowledged. RS in patients with AECOPD were recorded within 24-48 h of hospital presentation, at a timing where the medication prescribed (systemic corticosteroids and antibiotics) had presumably some beneficial effects on lung function. Moreover, the inclusion of patients with mild to moderate AECOPD may have also influenced the results. Probably, more remarkable differences would have been found if patients with stable COPD were compared to patients with AECOPD at the moment of hospital presentation or with severe exacerbations. In addition, an analysis of the RS in patients with AECOPD after recovery could have been performed to see if their RS became similar to those from patients with stable COPD. This would clarify if patients with AECOPD have indeed more adventitious RS than stable patients, or instead if patients with COPD more predisposed to exacerbations have already more adventitious RS during stable periods than patients with lower exacerbation rates. Moreover, in future research, it would also be interesting to compare computerized RS at stable and exacerbation periods within the same subjects. This would eliminate the bias due to the high intersubject variability of RS (Jácome & Marques, 2015a). It could be hypothesized that the detection of crackles and wheezes may have been influenced by the airflow selected. Nevertheless, in a recent study with patients with COPD, these computerized RS were not significantly different across distinct airflows (Jácome & Marques, 2015a). This study was conducted with a small sample of each COPD grade, therefore it was not possible to determine whether the severity of the disease impacted on the results. Further research with larger samples is necessary to investigate the RS differences on each COPD grade. The complex set up used to record RS and airflow can also be seen as a limitation of the study and restricts the application of computerized RS in more severe

patients and particularly in acute clinical settings. As computerized RS shows promise, research should focus in developing technological solutions to acquire RS and airflow with minimal setup.

## Conclusion

Using computerized auscultation, it was found that crackles and wheezes are more frequent in patients with an AECOPD than in patients with stable COPD. Furthermore, the findings also indicate that, in the absence of time to perform a complete pulmonary auscultation, computerized auscultation of the posterior chest provides the most relevant clinical information. These findings suggest that computerized RS can contribute to the objective diagnosis and/or monitoring of AECOPD, which is especially valuable considering that this information can be obtained by integrating computerized techniques with pulmonary auscultation, a quickly, easily and non-invasive method, that is a routine component of the patients' physical examination.

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Study V

# Computerized respiratory sounds: novel outcomes for pulmonary rehabilitation in COPD

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Submitted to Lung

## Abstract

**Purpose:** Computerized respiratory sounds (CRS) are a simple and noninvasive measure to assess lung function. Nevertheless, their potential to detect changes in lung function after pulmonary rehabilitation (PR) is unknown and needs clarification if respiratory acoustics are to be used in clinical practice. Thus, this study investigated the short- and mid-term effects of PR on CRS in patients with COPD.

**Methods:** 41 patients with COPD completed a 12-week PR program and a 3-month follow-up. Conventional outcome measures included dyspnea, selfreported sputum, FEV<sub>1</sub>, exercise tolerance, self-reported physical activity, healthrelated quality of life and peripheral muscle strength. CRS were recorded at right/left posterior chest using two stethoscopes. Airflow was recorded with a pneumotachograph. Normal respiratory sounds, crackles and wheezes were analyzed with validated algorithms.

**Results:** There was a significant effect over time in all conventional outcomes, with the exception of FEV<sub>1</sub>. Inspiratory and expiratory median frequency of normal respiratory sounds in the 100-300Hz band were significantly lower immediately (MD=-2.3Hz, 95%CI -4 $\rightarrow$ -0.7 and MD=-1.9Hz, 95%CI -3.3 $\rightarrow$ -0.5) and at 3-months (MD=-2.1Hz, 95%CI -3.6 $\rightarrow$ -0.7 and MD=-2Hz, 95%CI - 3.6 $\rightarrow$ -0.5) post-PR. In addition, mean number of expiratory crackles (MD=-0.8, 95%CI -1.3 $\rightarrow$ -0.3) and inspiratory wheeze occupation rate (median 5.9 vs 0) were significantly lower immediately post-PR.

**Conclusions:** CRS are sensitive to short- and mid-term effects of PR in patients with COPD. These findings are encouraging for the clinical use of respiratory acoustics. Future research is needed to strengthen these findings and explore the potential of CRS to assess the effectiveness of other clinical interventions in COPD.

## Introduction

Chronic obstructive pulmonary disease (COPD) affects 210 million people worldwide (World Health Organization, 2007), placing a substantial burden on healthcare systems (Hilleman, Dewan, Malesker, & Friedman, 2000; Miravitlles, Murio, Guerrero, & Gisbert, 2003). According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD), COPD is characterized by a persistent and progressive airflow limitation, but also by its systemic consequences, mainly exacerbations and comorbidities (GOLD, 2016). Clinical manifestations are thus highly variable and no single outcome is able to capture the variety of pathological effects or assess the effectiveness of therapeutic interventions (Jones & Agusti, 2006).

In line with this evidence, the latest American Thoracic Society/European Respiratory Society research statement in COPD recognizes that there is increasing emphasis on using patient-centered outcomes in clinical research and supports their use to inform judgments related to patient care (Celli et al., 2015). It also recommends the identification of high-quality surrogate outcomes, as these outcomes are readily measured, provide information about disease progression and at the same time make research easier, more efficient and less costly (Celli et al., 2015). Therefore, according to this statement, the effectiveness of interventions in COPD should be established using both patient-centered and surrogate outcomes.

Pulmonary rehabilitation (PR) is an intervention considered to be one of the core components of the management of patients with COPD (Spruit et al., 2013). Patient-centered outcomes, namely health-related quality of life, exercise capacity and dyspnea, have been identified as the most important outcomes of PR (Spruit et al., 2014). Surrogate outcomes, such as rectus femoris crosssectional area, fat-free mass and the forced expiratory volume in 1 second (FEV<sub>1</sub>), have also been used to assess the effects of PR (Camp, Appleton, & Reid, 2000; Jones & Agusti, 2006; Menon et al., 2012; van Wetering, Hoogendoorn, Mol, Rutten-van Molken, & Schols, 2010). However, unlike the others outcomes, the FEV<sub>1</sub> has not been found to be responsive to PR (Camp et al., 2000; Jones & Agusti, 2006). Based on this evidence, and in the absence of other globally accepted surrogate outcome for lung function, it has been generally established that PR does not improve lung function in COPD (Spruit et al., 2013). Nevertheless, FEV<sub>1</sub> mainly reflects structural changes in the large airways (Annesi et al., 1992) and it is well-recognized that COPD primarily targets small airways (Vestbo et al., 2013). Hence, there is a need to explore new surrogate outcomes to assess the effects of PR on lung function.

Computerized respiratory sounds are a simple, objective and non-invasive surrogate measure to assess the function of the respiratory system (Bohadana, Izbicki, & Kraman, 2014). Respiratory sounds, namely normal and adventitious respiratory sounds (e.g.,crackles and wheezes), are directly related to movement of air, changes within lung morphology and presence of secretions (Bohadana et al., 2014; Kiyokawa & Pasterkamp, 2002). In patients with COPD, it has been shown that the number of detected wheezes, as well as their frequency, during forced expiratory maneuvers decreased after inhalation of terbutaline (Fiz et al., 2002). It has also been demonstrated that it is possible to characterize the course of acute exacerbations of COPD in two different respiratory sound patterns based on the variation of spectral parameters (Sánchez Morillo, Astorga Moreno, Fernández Granero, & León Jiménez, 2013). From the limited evidence, it can be hypothesized that computerized respiratory sounds have potential to detect changes in lung function after PR. However, this is unknown as this measure has never been used to assess this intervention.

Thus, this study primarily aimed to investigate the short- and mid-term effects of PR on computerized respiratory sounds in patients with COPD. The secondary aim was to explore correlations between computerized respiratory sounds and patient-centered outcomes.

# Methods

#### Design and Participants

This was a one-arm longitudinal study investigating the effects of PR on computerized respiratory sounds in patients with COPD. A control group was not included as respiratory sounds show high inter-subject variability among patients with COPD (Jácome & Margues, 2015a). Instead, throughout the study, each patient serve as his/her own control to examine the effects of PR on computerized respiratory sounds. Patients with COPD were recruited from two primary care centers. Inclusion criteria were i) diagnosis of COPD according to the GOLD (Vestbo et al., 2013), ii) age  $\geq$ 40 years old and iii) clinical stability for 1 month prior to the study (i.e., no hospital admissions or exacerbations as defined by the GOLD or changes in medication for the respiratory system) (Vestbo et al., 2013). Patients were excluded if they presented severe psychiatric, neurologic or musculoskeletal conditions (Nici & ZuWallack, 2010) and/or unstable cardiovascular disease that could interfere with their performance during the exercise training sessions. The study was approved by the Center Health Regional Administration (2013-05-02) and from the National Data Protection Committee (3292/2013). Eligible patients, identified via clinicians, were contacted by the researchers, who explained the purpose of the study and asked about their willingness to participate. When patients agreed to participate, an appointment with the researchers was scheduled. Written informed consent was obtained prior to data collection.

#### Intervention

The PR program was held for 12 weeks and was composed of 3 weekly sessions of exercise training and 1 weekly session of psychoeducation. A detailed description of the program is provided elsewhere (Jácome & Marques, 2014).

## Data Collection

Data were collected before and immediately after PR and then at 3-months post-PR. Two baseline computerized respiratory sound recordings with a 1-week

interval before the intervention (hereafter referred to as baselines 1 and 2) were collected. This was performed to confirm the stability of patients' respiratory acoustics. A similar procedure have been performed with other biosignals that support clinical decisions (e.g., heart rate, arterial pressure, magnetic resonance imaging) (Ahern et al., 2001; Jafari-Khouzani et al., 2015; Thooft et al., 2011). At baseline 1, socio-demographic, anthropometric (height and weight) and clinical (smoking habits, exacerbations in the previous year) data were first obtained. Dyspnea was assessed with the Modified Medical Research Council (mMRC) questionnaire (Vestbo et al., 2013). Then, computerized respiratory sounds were recorded.

Dyspnea at rest, self-reported sputum, computerized respiratory sounds, lung function, exercise tolerance, self-reported physical activity, health related quality of life and peripheral muscle strength were assessed at baseline 2 (immediately pre-PR), immediately post-PR and at 3-months post-PR. Patients' were classified using both the GOLD spirometric classification (mild, moderate, severe-to-very severe) and the GOLD combined assessment (A, B, C and D) (Vestbo et al., 2013). All assessments were performed by two physiotherapists and the order was standardized.

# **Outcome Measures**

Conventional outcome measures

Dyspnea

Dyspnea at rest was assessed with the modified Borg scale (Borg, 1970). Patients were asked to rate their dyspnea from 0 to 10. This scale is frequently used to assess the effect of PR as it has been shown to be reliable, valid and responsive (Spruit et al., 2013).

# Self-reported sputum

Self-reported sputum was assessed using a numerical rating scale from 0 to 10 anchored at either end with a statement ('no sputum at all'=0; 'the worst sputum imaginable'=10). Patients were asked to select the number that best represented their subjective perception. Numerical rating scales have shown to

have better responsiveness and to be easier to use than verbal rating scale or visual analogue scales (Hjermstad et al., 2011).

## Lung function

A spirometric test, using a portable spirometer (MicroLab 3500, CareFusion, Kent, UK), was performed according to standardized guidelines (Miller et al., 2005).

## Exercise tolerance

Exercise tolerance was measured using the 6-minute walk test (6MWT). Two tests were performed according to the protocol described by the American Thoracic Society (American Thoracic Society, 2002) and the best performance was considered.

### Peripheral muscle strength

The knee extensors muscle strength of the dominant limb was determined by 1 repetition maximum (Multigym Plus G112X, Vitoria-Gasteiz, ES) (American College of Sports Medicine, 2009).

### Self-reported physical activity

The brief physical activity assessment was used as it is recommended for patients with COPD (Royal Dutch Society for Physical Therapy, 2008). It consists of two questions assessing the frequency/duration of vigorous and moderate physical activity undertaken in a "usual" week (Marshall, Smith, Bauman, & Kaur, 2005). A score higher or equal to 4 indicates that the patient is sufficiently active (Marshall et al., 2005).

## Health-related quality of life

The St George Respiratory Questionnaire (SGRQ), with its three domains (symptoms, activities and impact), is one of the most widely used disease-specific questionnaire to assess the impact of PR on health-related quality of life (Spruit et al., 2013). Scores range from 0 (no impairment) to 100 (maximum impairment). In this study only the SGRQ total and the symptoms scores were analyzed. SGRQ symptoms was the only sub-domain analyzed due to the described

relationship between respiratory sounds and movement of air, changes within lung morphology and presence of secretions (Bohadana et al., 2014; Kiyokawa & Pasterkamp, 2002).

# Novel outcome measures

# Computerized respiratory sounds

After 5-min of quiet sitting, airflow and respiratory sounds were acquired simultaneously during 20 seconds (Vyshedskiy & Murphy, 2012). Patients were in a seated-upright position, wearing a nose clip and breathing through a mouthpiece connected to a heated pneumotachograph (3830, Hans Rudolph, Inc., Shawnee, KS, USA). A peak airflow of 0.4–0.6 I/s was selected as computerized respiratory sounds have been shown to be reliable at this airflow range in patients with COPD (Jácome & Marques, 2015a). Patients had visual biofeedback of the flow signal (RSS 100R Research Pneumotach System, Hans Rudolph, Shawnee, KS, USA) and were instructed to maintain the flow between two horizontal lines. Recording was preceded by a training phase of at least 3 breathing cycles.

Recordings were performed simultaneously at right and left posterior chest (5 cm laterally from the paravertebral line and 7 cm below the scapular angle)(Sovijarvi, Vanderschoot, & Earis, 2000) using the LungSounds@UA interface (Pinho, Oliveira, Oliveira, Dinis, & Marques, 2014). Two chest pieces (Classic II S.E., Littmann®, 3M, St. Paul, MN, USA), with a microphone (frequency response between 20Hz and 19kHz - TOM-1545P-R, Projects Unlimited, Inc.®, Dayton, OH, USA) and preamplifier circuit (Intelligent Sensing Anywhere®, Coimbra, PT) in the main tube, were attached to the patient's skin with adhesive tape (Soft Cloth Surgical Tape, 3M, St. Paul, MN, USA). The analogue sound signals were further amplified and converted to digital by an audio interface (M-Audio® ProFire 2626, Irwindale, CA, USA). The signal was converted with a 24-bit resolution at a sampling rate of 44.1kHz and recorded in .wav format.

All generated files were processed using algorithms written in Matlab®R2009a (Mathworks, Natick, MA, USA). Breathing phases were automatically detected using the positive and negative airflow signals. Mean inspiratory and expiratory time were then calculated. The mean airflows and tidal volumes were calculated per breathing phase using flow and volume raw signals. The flow was timed synchronized with the sound to combine the detected breathing phases with sound signals.

Crackles are adventitious, discontinuous and explosive sounds (Sovijärvi et al., 2000) and were detected using a multi-algorithm technique based on established algorithms (Hadjileontiadis & Rekanos, 2003; Lu & Bahoura, 2008; Vannuccini, Rossi, & Pasquali, 1998). This multi-algorithm technique showed a 7% performance improvement over the best individual algorithm (Quintas, Campos, & Marques, 2013). Wheezes are adventitious, continuous (≥100 ms) sounds with a musical character (dominant frequency usually over 100 Hz) (Sovijärvi et al., 2000). This type of adventitious respiratory sound was detected using an algorithm based on time-frequency analysis (Taplidou & Hadjileontiadis, 2007). The mean number of crackles and the wheeze occupation rate per breathing phase (inspiration and expiration) and per chest location (right and left posterior chest) were extracted.

Normal respiratory sounds at the chest wall have low-frequency during inspiration and are hardly audible during expiration (Sovijärvi et al., 2000). Normal respiratory sounds were analyzed based on the methodology proposed by Pasterkamp (Pasterkamp, Powell, & Sanchez, 1996), after excluding adventitious respiratory sounds (crackles and wheezes). The median frequency (F50) and the mean intensity were determined for the two most commonly analyzed frequency bands, i.e., 100 to 300 Hz and 300 to 600 Hz and extracted per breathing phase and per chest location (Pasterkamp et al., 1996; Sanchez & Vizcaya, 2003).

## Statistical Analysis

A power calculation was not performed since there is no published data using computerized respiratory sounds to assess the effects of PR in patients with COPD. Descriptive statistics were used to describe the sample and to examine the outcome measures. Differences between patients who completed the study and dropouts were tested using independent *t*-tests for continuous normally distributed data, Mann-Whitney *U* tests for continuous non-normally distributed data and chi-square tests for categorical data (Elliott & Woodward, 2007).

Computerized respiratory sounds were explored between right and left posterior chest, however, no significant differences were found. Hence, data from both locations were pooled to simplify the interpretability of the findings.

Computerized respiratory sounds and breathing pattern (inspiratory/expiratory airflow, volume and time) parameters were compared between baseline 1 and baseline 2 with paired t-tests for normally distributed data or Wilcoxon signed-rank test for non-normally distributed data. After confirming that there were no significant differences, baseline 2, hereafter referred as baseline, was used for further analysis.

Patients were considered to have crackles or wheezes if they had at least a mean of one crackle/wheeze at baseline. To investigate differences in the number of patients with crackles/wheezes across time points the Cochran Q test was used and the Kendall's coefficient of concordance (Kendall's W) was reported as estimate of effect size (Rovai, Baker, & Ponton, 2014). This coefficient was interpreted as follows: very weak (0-0.20), weak (0.20-0.40), moderate (0.40-0.60), strong (0.60-0.80) and very strong (0.80-1.00) effect (Rovai et al., 2014). If the effect of time was significant, pairwise comparisons were performed using Bonferroni correction (Elliott & Woodward, 2007).

Normality was verified for all outcome measures (Kim, 2013). When data were normally distributed, one-way analysis of variance with repeated measures was used to establish the effects of time (Elliott & Woodward, 2007). The effect size was computed via Partial eta-squared as it is the index more commonly reported in the analysis of variance (Levine & Hullett, 2002). Partial eta-squared

 $(\eta^2)$  was interpreted as a small ( $\geq 0.01$ ), medium ( $\geq 0.06$ ) or large ( $\geq 0.14$ ) effect (Cohen, 1969). When the effect of time was significant, post hoc analyzes were conducted with pairwise comparisons using the Bonferroni correction to assess differences across the three time points (baseline, post-PR and 3-months post-PR).

When data were not normally distributed, the Friedman test was used, together with the effect size estimate Kendall's W (Rovai et al., 2014). If the effect of time was significant, post hoc analyzes were conducted with Wilcoxon signed-rank tests using Bonferroni correction.

As relationships between computerized respiratory sounds (F50, mean intensity, mean number of crackles and wheeze occupation rate) and conventional outcome measures are yet little understood, correlations with Pearson's coefficient ( $r_p$ ) or Spearman's rho ( $r_s$ ) were explored (Elliott & Woodward, 2007).

Differences on breathing parameters across time were also explored with one-way analysis of variance for repeated measures, as the breathing pattern can play a role in the genesis of normal (Gavriely & Cugell, 1996) and adventitious respiratory sounds (Meslier, Charbonneau, & Racineux, 1995; Nath & Capel, 1974; Vyshedskiy et al., 2009).

Statistical analyzes were performed using IBM SPSS Statistics version 20.0 (IBM Corporation, Armonk, NY, USA) and plots were created using GraphPad Prism version 5.01 (GraphPad Software, Inc., La Jolla, CA, USA). The level of significance was set at 0.05.

# Results

## Participants

A total of 51 participants were enrolled, however the final sample comprised 41 participants (Figure 1).



Figure 1. Flow of participants throughout the study.

Participants were mostly male (85.4%), had a mean age of  $67\pm8.8$  years old and a mean FEV<sub>1</sub> of  $68.9\pm21.7\%$  of the predicted (Table 1). There were no significant differences between completers and dropouts with regard to any of the baseline characteristics (p>0.05).

## Conventional outcome measures

There was a significant effect over time in all conventional outcomes (p<0.007;  $\eta^2$  from 0.121 to 0.609), with the exception of FEV<sub>1</sub> (p=0.156) (Table 2).

Characteristics	
Sex (male), n (%)	35 (85.4)
Age (years)	67 ± 8.8
Current smokers	8 (19.5)
BMI (kg/m²)	28.9 ± 3.6
mMRC, M [IQR]	1 [1, 2]
FEV <sub>1</sub> (L)	1.9 ± 0.6
FEV1 (% predicted(Quanjer et al., 2012))	68.9 ± 21.7
FEV <sub>1</sub> /FVC	0.6 ± 0.1
GOLD spirometric classification, n (%)	
Mild	17 (41.5)
Moderate	16 (39)
Severe-to-very-severe	8 (19.5)
GOLD combined assessment, n (%)	
A	14 (34.1)
В	15 (36.6)
C & D	12 (29.3)
N=41	

Table 1. Sociodemographic and clinical characteristics of participants

Values are shown as mean±standard deviation unless otherwise indicated. Values are shown as mean±standard deviation unless otherwis mMRC, modified Medical Research Council questionnaire; M, median; IQR, interquartile range; BMI, body mass index; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

Table 2. Conventional outcome measures to assess pulmonary rehabilitation across time

Outcome measure	Baseline	Immediately	3-months Post-	р	η²
		Post-PR	PR		
Dyspnea (0-10)	1 [0,2]	1 [0,2]*	0 [0, 1.75]*	0.007	0.121
Sputum (0-10)	1.5 [0, 4]	1 [0, 2]*	1 [0, 2]*	0.003	0.154
FEV1 (% predicted(Quanjer et al., 2012))	68.9±21.7	67.1±21.8	68±21.7	0.156	0.049
6MWD (m)	481.3±76.1	538.8±78.8*	525.2±75.5 <sup>*, #</sup>	<0.001	0.514
Knee extensors (kg)	37.9±8.5	47.5±11.5*	41.8±11.1* <sup>, #</sup>	<0.001	0.609
Physical activity (0-8)	1.8±2.0	5.1±1.6*	3.4±2.3 <sup>*, #</sup>	<0.001	0.445
SGRQ total (0-100)	31.0±16.8	24.2±17.6*	22.1±12.1*	<0.001	0.271
SGRQ symptoms (0-100)	40.6±20.8	33.0±18.8*	27.3±20.0*	0.003	0.140

N=41

N=41 Data are presented as mean±standard deviation. Significantly different from baseline (\*) and from post-PR (#). 6MWD, 6-minute walk distance; FEV<sub>1</sub>, forced expiratory volume in one second PR, pulmonary rehabilitation SGRQ, St. George's Respiratory Questionnaire η<sup>2</sup>, partial eta-squared.

## Novel outcome measures

Normal respiratory sounds

The inspiratory and expiratory F50 of normal respiratory sounds changed only in the 100 to 300Hz band (p=0.006,  $\eta^2$ =0.061 and p=0.012,  $\eta^2$ =0.054) (Figure 2). Inspiratory F50 was significantly lower immediately after PR and at 3months post-PR compared to baseline (MD=-2.3(95%CI -4 $\rightarrow$ -0.7)Hz, p=0.006 and MD=-2.1(95%CI -3.6 $\rightarrow$ -0.7)Hz, p=0.005). Similar changes were observed in expiratory F50 compared to baseline (MD=-1.9(95%CI -3.3 $\rightarrow$ -0.5)Hz, p=0.010 and MD=-2(95%CI -3.6 $\rightarrow$ -0.5)Hz, p=0.009).

No significant differences were seen in the 300 to 600Hz band (inspiration p=0.422 and expiration p=0.567) (Figure 2). Also no significant differences in the mean intensity of normal respiratory sounds (p>0.05) were found (Figure 2). Means and standard deviations of F50 and mean intensity at each time point are presented in table 3.



Figure 2. Median frequency (F50 – A and B) and mean intensity (Imean – C and D) of normal respiratory sounds at two frequency bands (100-300Hz and 300-600Hz) across time. Data are presented as mean  $\pm$  95% confidence intervals. Significant different from baseline(\*). PR, pulmonary rehabilitation; 3M, 3-months.

Immediately post-PR, there were weak-to-moderate relationships between inspiratory F50 (300 to 600Hz band) and SGRQ symptoms ( $r_p=0.57$ ; p<0.001), SGRQ total ( $r_p=0.52$ ; p=0.001), rest dyspnea ( $r_p=0.41$ ; p=0.008) and self-reported sputum ( $r_p=0.33$ ; p=0.039).

## Crackles

All patients had inspiratory crackles across the different time points, however the frequency of patients with expiratory crackles decreased across time (p=0.005; Kendall's W=0.129). Expiratory crackles were present in all patients before the intervention whereas after PR expiratory crackles were found in 34 (82.9%; p=0.004) patients and at 3-months post-PR in 37 (90.2%; p=0.192) patients. Also no significant difference was found in the frequency of patients with expiratory crackles between post-PR and 3-months post-PR (p=0.495).

The mean number of inspiratory crackles did not change significantly across time (p=0.511) (Figure 3). Expiratory crackles, however, changed across the three time points (p=0.013;  $\eta^2$ =0.068). Their mean number was significantly lower immediately after PR, compared to baseline (MD=-0.8(95%CI -1.3 $\rightarrow$ -0.3), p=0.003) (Figure 3). Means and standard deviations of crackles at each time point are presented in table 3.



Figure 3. Mean number of inspiratory (A) and expiratory (B) crackles across time. Data are presented as mean±95% confidence intervals. Significant different from baseline (\*). PR, pulmonary rehabilitation; 3M, 3-months.

After PR, weak-to-moderate positive relationships were found between the mean number of inspiratory ( $r_p=0.4$ ; p=0.010) and expiratory ( $r_p=0.33$ ; p=0.036) crackles and rest dyspnea. No other relationships were found.

#### Wheezes

The frequencies of patients with inspiratory (p=0.006, Kendall's W=0.083) and expiratory (p=0.002; Kendall's W=0.097) wheezes were different across time points. Twelve (29.3%) patients presented inspiratory and 17 (41.5%) expiratory wheezes before the intervention, whereas immediately after PR they were only 6 (14.6%; p=0.060) and 9 (22%; p=0.014) and at 3-months post-PR, 4 (9.8%; p=0.006) and 8 (19.5%; p=0.004), respectively. No significant differences were observed in the frequency of patients with inspiratory/expiratory wheezes between post-PR and 3-months post-PR (p=1).

Figure 4 shows the behavior of wheeze occupation rate over time of patients with wheezes at baseline. Inspiratory wheeze occupation rate changed across the three time points (p<0.001; Kendall's W=0.514). Post hoc analysis was conducted with a Bonferroni correction. Inspiratory wheeze occupation rate was significantly lower after PR (median 0) compared to the baseline (median 5.9, p=0.001). Expiratory wheeze occupation rate changed significantly across time (p<0.003; Kendall's W=0.314), however, during post-hoc tests no significant results were found. Only a tendency for lower expiratory wheeze occupation rate after PR (median 0.8) compared to baseline (median 8.9) (p=0.035) was observed (Figure 4). Medians and interquartile ranges of wheeze occupation rate at each time point are presented in table 3.



Figure 4. Wheeze occupation rate during inspiration (A) and expiration (B) across time. Data are presented as box and whisker plots with median, interquartile ranges and 5-95% percentiles. Significant different from baseline (\*). PR, pulmonary rehabilitation; 3M, 3-months.

In patients with no inspiratory (n=29; 70.7%) or expiratory (n=24; 58.5%) wheezes at baseline, no significant differences in the behavior of inspiratory (medians of 0 at baseline, post-PR and 3-months post-PR; p=0.766) or expiratory (medians of 0 at baseline and 3-months post-PR and median of 2 post-PR; p=0.535) wheeze occupation rates were found across the three time points.

A moderate correlation between expiratory wheeze occupation rate and FEV<sub>1</sub> was verified ( $r_s$ =-0.35; p=0.028) before the intervention. No other relationships were found.

## Breathing pattern

No significant differences over time were observed on inspiratory/expiratory flow (p=0.057 and p=0.124), volume (p=0.140 and p=0.178) or time (p=0.478 and p=0.577) during the recordings of respiratory sounds (Figure 5). Means and standard deviations of breathing pattern parameters at each time point are presented in table 3.



Figure 5. Inspiratory and expiratory flow (A), volume (B) and time (C) across time. Data are presented as mean ± 95% confidence intervals. PR, pulmonary rehabilitation; 3M, 3-months.

Outcome measures	Baseline	Immediately	3-months	р	η²
		Post-PR	Post-PR		
Inspiratory normal respiratory sounds					
F50 100-300Hz	55.4±5.5	53.0±6.7	53.2±6.0	0.006	0.061
F50 300-600Hz	86.0±10.8	85.9±9.5	87.6±10.4	0.422	0.012
Imean 100-300Hz	8.5±1.9	8.5±1.7	8.3±1.7	0.517	0.008
Imean 300-600Hz	6.7 ±1.7	6.7±1.6	6.8±1.5	0.681	0.005
Expiratory normal respiratory sounds					
F50 100-300Hz	52.7±5.2	50.8±6.1	50.6±6.3	0.012	0.054
F50 300-600Hz	83.8±11.4	82.7±8.7	84±9.9	0.567	0.008
Imean 100-300Hz	8±1.7	7.6±1.3	7.9±2	0.142	0.024
Imean 300-600Hz	6±1.8	5.4±1.8	5.8±1.7	0.095	0.057
Inspiratory crackles	2.6±1.7	2.9±2.6	2.6±2.2	0.511	0.010
Expiratory crackles	2.9±2.2	2.1±1.8	2.5±2.2	0.013	0.068
Inspiratory Wh%, M [IQR]	5.9 [2.8, 13]	0 [0, 2.7]	0 [0, 3.3]	<0.001	0.514
Expiratory Wh%, M [IQR]	8.9 [2.6, 15.1]	0.8 [0, 5.1]	0 [0, 9.6]	0.003	0.314
Breathing pattern parameters					
Inspiratory flow	0.5±0.2	0.6±0.1	0.5±0.1	0.057	0.122
Expiratory flow	0.4±0.1	0.5±0.1	0.5±0.2	0.124	0.077
Inspiratory volume	0.6±0.3	0.7±0.2	0.7±0.2	0.140	0.068
Expiratory volume	0.6±0.3	0.7±0.2	0.7±0.2	0.178	0.058
Inspiratory time	1.1±0.5	1.1±0.4	1.2±0.4	0.478	0.23
Expiratory time	1.2±0.7	1.4±0.6	1.4±0.5	0.452	0.025

Table 3. Results of the novel outcome measures to assess pulmonary rehabilitation across time

N=41 Values are shown as mean±standard deviation unless otherwise indicated. F50, median frequency; Imean, mean intensity;

M, Median;

PR, pulmonary rehabilitation; Wh% - wheeze occupation rate;

η<sup>2</sup>, partial eta-squared.

## Discussion

To the best of authors' knowledge, this was the first study investigating the effects of PR on computerized respiratory sounds in patients with COPD. The main findings indicated that F50 of normal respiratory sounds, number of crackles and wheeze occupation rate were able to detect significant differences in lung function immediately post-PR and that most of these effects were not maintained after 3 months.

The F50 of normal respiratory sounds was sensitive to PR, while intensity remained unchanged. Similar observations were reported by Malmberg et al. which found respiratory sounds intensity at standardized airflows to be less informative than the F50 as an indicator of flow obstruction in adults with asthma and healthy subjects (Malmberg et al., 1994). Morillo et al. (2013) also found that F50 was one of the respiratory sounds parameters to better distinguish between two groups of patients with acute exacerbation of COPD (Sánchez Morillo et al., 2013). Inspiratory and expiratory F50 were significantly lower immediately and at 3-months post-PR. To the authors' knowledge, no published studies have tested the change in normal respiratory sounds after PR. Previous studies have demonstrated that higher F50 are related with pathologic events, such as bronchoconstriction and presence of pneumonia (Malmberg et al., 1994; Sánchez Morillo et al., 2013) and therefore, the decrease in F50 found in this study may reflect an improvement of lung function after PR. This decrease was only significant in the 100 to 300 Hz band, possibly because this frequency band is where, in stable conditions, most of the acoustic energy resides (Bohadana et al., 2014; Pasterkamp, Kraman, & Wodicka, 1997). Nevertheless, as bronchoconstriction and sputum generate flow-turbulent noise, and flow turbulence produce sounds in high frequency ranges (Pasterkamp & Sanchez, 1996), the frequency band of 300-600 Hz is also of clinical importance. Positive relationships between inspiratory F50 and patients' symptoms (SQRQ symptoms, rest dyspnea, self-reported sputum) and health-related quality of life (SGRQ total) were only found at this high frequency band (300-600 Hz). Future

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studies assessing the effects of PR on normal respiratory sounds of patients with acute exacerbation of COPD should therefore consider both low and high frequency bands.

The mean number of inspiratory crackles did not change across time. This result was somewhat expected as it is well-known that COPD is characterized by inspiratory crackles (Jácome & Marques, 2015b; Piirila & Sovijarvi, 1995). Moreover the mean number of inspiratory crackles at the three time points was within the range of previously reported results (Jácome, Oliveira, & Margues, 2015; Murphy, 2008; Piirila, 1992). The mean number of expiratory crackles, however, was significantly lower immediately after PR. No studies have investigated the change in number of crackles in patients with COPD after PR. Nevertheless, this result agree with the findings from Piirila (1992), which also observed a slight decrease in the number of expiratory crackles (from  $0.8 \pm 0.8$ to  $0.7 \pm 0.1$ ) after standard medical treatment in 11 patients with pneumonia (Piirila, 1992). After PR the slight, but consistent, reduction in the number of expiratory crackles can be due to a combination of a number of factors. First, the active airway clearance techniques practiced during the PR program may have enhanced sputum evacuation (Ides, Vissers, De Backer, Leemans, & De Backer, 2011; Mikelsons, 2008). A systematic review about the use of airway clearance techniques in patients with COPD found that active airway clearance techniques were effective to remove secretions (Ides et al., 2011). Second, the participation in the PR program may have optimized the use of maintenance bronchodilator therapy (Spruit et al., 2013) and it is known that bronchodilators act on airway smooth muscle, reducing air trapping and hyperinflation (O'Donnell et al., 2004; Ramirez-Venegas, Ward, Lentine, & Mahler, 1997). Less sputum and reduced hyperinflation may have altered airway diameter and characteristics (Pasterkamp et al., 1997; Vyshedskiy, Ishikawa, & Murphy, 2011) possibly causing less sudden airway closing events during expiration. Despite the possible explanatory reasons, the decrease in the mean number of expiratory crackles after PR seem to point out to an improvement of patients' lung function after PR. A recent study showed that expiratory crackles are significantly more frequent during periods of increased disease severity (acute exacerbations of COPD) than stable periods (median 3.17 vs. 0.83) (Jácome et al., 2015). Additionally, a positive correlation was found between crackles and rest dyspnea. To date, there are no references in the literature about this correlation. It is believed, however, that hyperinflation may explain this relationship, as it is fundamental to the origin of dyspnea (Laveneziana, Parker, & O'Donnell, 2007) and contributes to crackles' genesis.

Inspiratory wheeze occupation rate was significantly lower after PR compared to the baseline. This result is in line with the study from Dinis et al. (2013) investigating the effect of 3 weeks of pharmacotherapy plus respiratory physical therapy in 9 patients with lower respiratory tract infection (Dinis et al., 2013). In this study, a significant decrease in inspiratory wheeze occupation rate (from 9.2  $\pm$  14.1% to 0.4  $\pm$  1.9%) was found (Dinis et al., 2013). In patients with asthma, inspiratory wheezes are associated with more severe airway obstruction than expiratory wheezes (Shim & Williams, 1983). Higher inspiratory wheeze occupation rate has also shown to be a characteristic of acute exacerbations of COPD (Jácome et al., 2015). Based on this evidence, it is possible that the significant decrease in inspiratory wheeze occupation rate reflects an improvement on participants' airway obstruction after PR. Wheeze occupation rate during expiration did not change with PR. Expiratory wheezes, in contrast with inspiratory wheezes, are a common sign in patients with COPD (Fiz et al., 2002; Murphy, 2008) and baseline values were in line with earlier studies (Murphy, 2008). It was also verified that severity of airflow limitation was correlated with expiratory wheeze occupation rate, with lower values of FEV1 producing higher wheeze occupation rate, as previously shown by Fiz et al. (2002).

No short- or mid-term improvement in FEV<sub>1</sub> was observed after PR, which is in agreement with previous studies (Foglio et al., 2007; Ries, Kaplan, Myers, & Prewitt, 2003). In light of this research, it has been established that PR does not improve lung function in COPD (Spruit et al., 2013). However, FEV<sub>1</sub> mainly reflects large airways (Annesi et al., 1992) and it is well-recognized that COPD primarily targets small airways (Vestbo et al., 2013). Moreover, FEV1 is only one possible parameter to measure lung function, inspiratory capacity, diffusing capacity and respiratory sounds parameters are examples of other possible surrogate outcomes (Jones & Agusti, 2006). In this study, the potential of computerized respiratory sounds for assessing the short-term effect of PR on lung function has been shown. This noteworthy finding demonstrates that respiratory sounds are a more sensitive indicator on the status of lung function, than FEV<sub>1</sub>, which is in line with the study from Gavriely et al. (1994) (Gavriely, Nissan, Cugell, & Rubin, 1994). In this study, half of patients with a history compatible with COPD had normal spirometry and abnormal respiratory sounds, revealing that airway abnormalities not detectable by standard spirometry generate abnormal acoustic signals (Gavriely et al., 1994). Our results also demonstrate that the effects of PR on respiratory sounds parameters start to decline at 3 months post-PR. With the conventional outcomes analyzed, however, at 3-months benefits were still significant compared to baseline. Therefore, it was shown that, in the absence of any maintenance strategy, the benefits of PR on lung function start to decline at 3 months post-PR, while the decrease on patient-centered outcomes will be noted later, usually over 6 months (Griffiths et al., 2000). This finding therefore points out to the importance of keeping patients motivated in changing behaviors after the program to maintain the benefits.

## Strengths and limitations

Recordings of respiratory sounds were made in the sitting position on two standardized chest locations, in line with the CORSA guidelines (Rossi et al., 2000). This will facilitate the comparison of these results with other studies. It could be argued that changes observed in normal and adventitious respiratory sounds after PR could be due to patients' breathing pattern changes. However, to account for this bias, airflow was standardized during all respiratory sound recordings. Moreover, an analysis of the breathing pattern parameters showed that no changes over time were observed. In addition, respiratory sounds were recorded at an airflow of 0.4–0.6 L/s, which has already been shown to be reliable

in patients with COPD (Jácome & Marques, 2015a). Nonetheless, the interpretation of the results from this study should be tempered considering the following limitations. To confirm the stability of patients' respiratory acoustics, two baseline computerized respiratory sound recordings were collected with only 1week interval. However, as symptoms in patients with COPD are characterized by weekly variability (Kessler et al., 2011) an additional recording (e.g., one month before the intervention) could have been performed. However, as no research has been conducted on this topic, this limitation does not appear to remove the validity and importance of the results found. Computerized respiratory sounds have high inter-subject variability among patients with COPD (Jácome & Marques, 2015a). However, to minimize the bias, each patient served as his/her own control. The sample included mainly individuals with early COPD (mild and moderate), and thus it was not possible to explore how the disease severity related to the sensitivity to change of respiratory sounds parameters. Future studies should use a more balanced sample of COPD grades to clarify these findings. This study only assessed the short- and mid-term effects of PR on computerized respiratory sounds, thus, the long-term effects of PR could not be established. Future studies with long-term follow-ups are therefore needed. The complex set up used to record respiratory sounds and airflow can also be seen as a limitation of the study and restricts the application of computerized respiratory sounds in day-to-day clinical practice. As computerized RS shows promise, research should focus in developing technological solutions to acquire RS and airflow with minimal setup.

### Conclusions

In conclusion, median frequency of normal respiratory sounds, mean number of crackles and wheeze occupation rate are able to detect significant differences in lung function after PR in patients with COPD. These findings suggest that computerized respiratory sounds parameters are sensitive outcomes to measure the short- and mid-term effects of PR in patients with
COPD. Future research is needed to strengthen these findings and to extend these observations to other clinical interventions and respiratory diseases.

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**Chapter IV** 

Discussion

### General discussion

This Thesis has focused on two areas where uncertainty regarding pulmonary rehabilitation in COPD remains: (1) the effectiveness of this intervention in patients with mild disease and (2) the effects of pulmonary rehabilitation on lung function assessed with computerized respiratory sounds. Although discussion of these areas has been presented in each study, an overall discussion aiming to provide the reader with a comprehensive perspective is followed.

### Pulmonary rehabilitation in mild COPD

Systematic review I summarized the evidence on pulmonary rehabilitation in mild COPD. Only three studies were included in this systematic review, being the oldest from 2004, demonstrating the new interest of pulmonary rehabilitation research in mild COPD. The design of the pulmonary rehabilitation programs implemented as well as the outcome measures used were described. A relevant conclusion was that pulmonary rehabilitation had significant positive effects on exercise capacity and health-related quality of life of patients with mild COPD. The inconclusive effects on use of health care resources and lung function were also discussed. The conclusions of this review contributed to the latest American Thoracic Society/European Respiratory Society policy statement on pulmonary rehabilitation, where this intervention is recommended for patients with mild COPD, with symptom-limited exercise tolerance (Rochester et al., 2015). Essentially, Systematic review I identified knowledge gaps that need to be bridge, specifically concerning the effects of pulmonary rehabilitation on other health domains, namely, dyspnea and muscle strength, in patients with mild COPD. In addition, only one of the included studies analyzed emergency department visits and hospitalization days one year after pulmonary rehabilitation, but no other data were available regarding the long-term benefits of pulmonary rehabilitation in mild COPD.

Studies I and II of this Thesis described the investigation on the feasibility and effectiveness of pulmonary rehabilitation in patients with mild COPD. The

observation that no adverse events occurred during or after pulmonary rehabilitation showed that this intervention is as feasible, safe and well tolerated for patients with mild as for moderate-to-severe COPD. The improvement on exercise tolerance (32-53 m in the 6MWT) and on health-related quality of life (~6 units in SGRQ total) after pulmonary rehabilitation in patients with mild COPD is consistent with the findings from previous studies (Golmohammadi, Jacobs, & Sin, 2004; Liu et al., 2012; Riario-Sforza et al., 2009) and similar to that found in patients with moderate-to-severe COPD (Beauchamp, Francella, Romano, Goldstein, & Brooks, 2013; Bestall et al., 2003; Egan et al., 2012; Karapolat et al., 2007; Spencer, Alison, & McKeough, 2010). Moreover, considering that 25 m and 4 units are the minimum clinically important differences in patients with COPD for the 6MWT (Holland et al., 2010) and for the SGRQ (Jones, 2005), respectively, it could be assumed that clinically important effects were achieved. Yet, this needs to be interpreted with caution as these minimum clinically important differences have been established based on samples of patients with a wide range of disease severity and thus, may not represent a clinically important effect for patients with mild COPD. Future research should determine the minimum clinically important differences for the 6MWT and SGRQ in patients with mild COPD to contribute to clinical decision making in this specific population. Nevertheless, these noteworthy findings demonstrated that exercise tolerance and health-related quality of life in patients with mild COPD, even if not severely affected, can be improved with early pulmonary rehabilitation. Benefits in dyspnea, peripheral muscle strength, self-reported physical activity and in the number of exacerbations were also found. Taken together, these findings confirm our hypotheses that pulmonary rehabilitation is effective in patients with mild COPD as well as in patients with moderate-to-severe COPD.

According to a clinical practice guideline of the most important societies in the field (American College of Physicians, the American College of Chest Physicians, the American Thoracic Society and the European Respiratory Society), pulmonary rehabilitation is currently recommended on the basis of FEV<sub>1</sub>, being strongly recommended for symptomatic patients with a FEV<sub>1</sub> less than 50% of the predicted and only weakly recommended for patients with a FEV1 greater than 50% predicted (Qaseem et al., 2011). However, our overall findings suggest that patients with FEV<sub>1</sub> greater than 80% of the predicted also benefit from pulmonary rehabilitation. Ergun et al. (2011) compared the effect of 8-week pulmonary rehabilitation program in a group of patients with early (mean FEV1 42.46% of the predicted) and advanced (mean FEV<sub>1</sub> 27.33% of the predicted) COPD and also found patients benefit from this comprehensive intervention regardless of the disease severity. Based on the current evidence, it may be of limited value to continue to rely on FEV<sub>1</sub> as a basis for prescribing pulmonary rehabilitation. In addition, the rational to use FEV1 seems paradoxical for three main reasons: (1) COPD is diagnosed on the basis of the unresponsiveness of FEV<sub>1</sub> (GOLD, 2016; Jones & Agusti, 2006); (2) FEV<sub>1</sub> has not been found to be responsive to pulmonary rehabilitation (Camp, Appleton, & Reid, 2000; Niederman et al., 1991; Ries, Kaplan, Limberg, & Prewitt, 1995); and (3) FEV<sub>1</sub> is not predictive of functional status nor disease progression (Nishimura, Izumi, Tsukino, & Oga, 2002; Vestbo et al., 2008). Therefore, despite the simplicity of FEV<sub>1</sub> in diagnosing and grading COPD, it may be the time to rethink the usefulness of FEV<sub>1</sub> as a criterion for pulmonary rehabilitation selection.

In line with this new evidence, the American Thoracic Society/European Respiratory Society policy statement recommends pulmonary rehabilitation not only for patients with moderate to severe airflow limitation, but also for those with mild to moderate airflow limitation with symptom limited exercise tolerance (Rochester et al., 2015). However, patients are not generally referred to pulmonary rehabilitation programs until they have moderate-to-severe COPD (Rochester et al., 2015; Spruit et al., 2013). This policy statement also recommends the development of novel pulmonary rehabilitation program models in order to increase patients' access to this intervention (Rochester et al., 2015). From our view, programs available at primary care or community centers could be a novel approach to deliver pulmonary rehabilitation to patients with mild COPD at a modest cost and using the existing resources. The biggest challenge would probably be the implementation of these programs in daily practice. In order to do so, all team members, including general practitioners, physical therapists and nurses, need to be believers and contributors to an early rehabilitation in primary care. An important future research direction is to investigate the cost-effectiveness of this community-based approach in patients with mild COPD compared to standard care. The need for further investigation regarding the cost-effectiveness of pulmonary rehabilitation has also been highlighted by the policy statement (Rochester et al., 2015).

Although data indicated that pulmonary rehabilitation should be a standard of care alongside other well-established treatments for patients with mild COPD (Jácome & Margues, 2014; Riario-Sforza et al., 2009), results also demonstrated that, similarly to what happens with patients with more advanced COPD (Bestall et al., 2003; Egan et al., 2012), the benefits in patients with mild COPD decline with time. This decline points out to the importance of keeping patients motivated in adhering to health-enhancing behaviors after the program to maintain its benefits. In patients with moderate-to-severe COPD, the benefits of pulmonary rehabilitation have been shown to be maintained for up to 1-year with a community-based maintenance exercise program, with minimal supervision from trained fitness instructors (Beauchamp et al., 2013). This method may also be effective in sustaining benefits of pulmonary rehabilitation in mild COPD and should be investigated in future research. Other strategies to promote longer lasting improvements in patients with mild COPD may include telephone followups, feedback on physical activity levels, telehealth-supported programs, among others, and offer a new research path for future studies.

# Computerized respiratory sounds as outcome measures

Systematic review II summarized the evidence of computerized respiratory sounds in COPD. It was found that normal respiratory sounds followed the pattern observed in healthy people; and adventitious respiratory sounds are mainly characterized by inspiratory crackles and expiratory wheezes. This systematic review included only seven studies with small samples demonstrating that the available evidence about computerized respiratory sounds in patients with COPD is limited. In addition, a lack of standardization across studies in the procedures used to record, analyze and characterize computerized respiratory sounds was underlined, which limited the interpretation and synthesis of the results. This was unexpected as guidelines for research and clinical practice in the field of respiratory sounds standardizing the nomenclature, instrumentation, ways of acquiring data, procedures and signal processing techniques have been available since 2000 (Sovijarvi, Vanderschoot, & Earis, 2000). Only recently an update has been published regarding respiratory sounds' nomenclature, which is now standardized in 29 languages (Pasterkamp et al., 2015). In order to address this gap in the literature, the original studies of this Thesis concerning computerized respiratory sounds (Studies III, IV and V) followed these international guidelines. The lack of studies comparing computerized respiratory sounds across patients with stable COPD with distinct characteristics (age, gender, disease grade, smoking history, etc.) was also highlighted. During exacerbations, however, it has already been shown that it is possible to characterize their course into two phenotypes based on the variation of specific respiratory sound characteristics (Sánchez Morillo, Astorga Moreno, Fernández Granero, & León Jiménez, 2013). Future research could investigate the existence of different phenotypes on computerized respiratory sounds in patients with stable and exacerbated COPD.

Reliability is an important issue in the conduct of clinical studies, as it provides information about the amount of error inherent in any measurement (Kottner et al., 2011). Thus, the reliability of computerized respiratory sounds was investigated in patients with COPD (Study III). Study III showed that normal respiratory sound intensity, mean number of crackles and wheezes are significantly different across distinct airflows in patients with COPD. These findings reinforce the need to use standardized airflows during computerized auscultation, mainly when it is aimed to compare computerized respiratory sounds at different time points. Unfortunately, this has not been a practice across studies (Fernandez-Granero, Sanchez-Morillo, & Leon-Jimenez, 2015; Marques, Bruton, Barney, & Hall, 2012; Piirila, 1992; Sánchez Morillo, Astorga Moreno, et

al., 2013). Nonetheless, this will be essential if computerized respiratory sounds are to become a surrogate outcome measure to evaluate the effectiveness of treatments. In addition, it was found that computerized respiratory sounds were more reliable at a target airflow of 0.4-0.6 L/s than at spontaneous airflow or at a target air flow of 0.7-1 L/s. Thus, future studies characterizing normal respiratory sounds, crackles, and wheezes in patients with COPD should use this standardized airflow. Still, even when recorded with the most reliable airflow, computerized respiratory sound parameters exhibited considerable inter-subject variability. High inter-subject variability of computerized respiratory sounds has also been reported previously in subjects with cystic fibrosis and bronchiectasis (Marques, Bruton, & Barney, 2009). This inter-subject variability may limit inferences at a group level, as respiratory sound patterns may fail to represent patterns seen in individuals. This advocates that health professionals should support their clinical decisions in the interpretation of individual respiratory sound changes and in combination with other clinical data. To overcome the high intersubject variability of computerized respiratory sounds, future research examining changes in respiratory acoustics should use cross-over designs, where each patient serve as his/her own control and thus, any component that is related to the differences between the subjects is removed from comparisons (Jones & Kenward, 2015). Study V of this Thesis was designed taking into account this limitation. A recently published study had also taken this into consideration (Fernandez-Granero et al., 2015). Fernandez-Granero et al. monitored computerized respiratory sounds in 16 patients with COPD during 6-months on a day-to-day basis to evaluate the feasibility of machine learning techniques for the remote early detection of acute exacerbations of COPD. Using this approach, 75.8% of the exacerbations were detected ~5 days in advance of medical attention (Fernandez-Granero et al., 2015).

Studies IV and V assessed the sensitivity to change of computerized respiratory sounds. Study IV explored differences in computerized respiratory sounds between patients with stable COPD and patients with acute exacerbation of COPD. The main findings indicated that adventitious respiratory sounds,

namely crackles and wheezes, are significantly more frequent in patients with acute exacerbation of COPD. During exacerbation periods, there is increased airway inflammation, which induces edema, bronchospasm and sputum production (O'Donnell & Parker, 2006). These airway changes will probably (1) alter airway diameter and characteristics (Pasterkamp, Kraman, & Wodicka, 1997; Vyshedskiy, Ishikawa, & Murphy, 2011), possibly causing more sudden airway opening/closing events – linked to crackle genesis; and (2) reduce the critical flutter velocity, producing oscillations of the airway walls more easily – genesis of wheezes (Meslier, Charbonneau, & Racineux, 1995). Nevertheless, to better understand our results, fundamental research investigating the genesis of adventitious respiratory sounds is urgently needed.

In Study IV, it was also found that the posterior chest was the most informative region. Posterior chest is a gravity-dependent region, where greater volume changes occur during inspiration (Pennati, Salito, Baroni, Woods, & Aliverti, 2014). In a study assessing changes in crackles before and after a single session of airway clearance therapy in patients with bronchiectasis, almost half (47%) of significant changes were also seen in the posterior locations (Margues et al., 2012). Thus, in the absence of time to perform a complete pulmonary auscultation, health professionals can rely on computerized auscultation of the posterior chest as this region provides the most relevant clinical information. Moreover, findings suggested that the detection of increased or decreased number of crackles and/or wheeze occupation rate may have the potential to contribute to the objective diagnosis of acute exacerbation of COPD, which would be of great value since currently diagnosis relies on patients' clinical presentation (GOLD, 2016). The overall findings extend previous research stating that computerized respiratory sounds can support the diagnosis of pneumonia, characterize and early detect acute exacerbations in patients with COPD (Fernandez-Granero et al., 2015; Sánchez Morillo, Astorga Moreno, et al., 2013; Sánchez Morillo, Leon Jimenez, & Moreno, 2013).

To our knowledge, Study V was the first to investigate the short- and midterm effects of pulmonary rehabilitation on computerized respiratory sounds. No previous data are available neither in COPD nor in other respiratory diseases. The main findings indicated that median frequency of normal respiratory sounds, number of expiratory crackles and inspiratory wheeze occupation rate were able to detect significant differences in lung function immediately post-PR and that most of these effects were not maintained after 3 months. Based on previous evidence (Dinis et al., 2013; Malmberg et al., 1994; Piirila, 1992; Sánchez Morillo, Astorga Moreno, et al., 2013) and on findings from Study IV, it is possible that the minor changes in computerized respiratory sounds after pulmonary rehabilitation reflect an improvement on patients' lung function. Nevertheless, this study renders more questions than answers. At this point in time, we can only speculate about the underlying reasons. Firstly, the active airway clearance techniques practiced during the pulmonary rehabilitation program may have enhanced sputum evacuation (Ides, Vissers, De Backer, Leemans, & De Backer, 2011; Mikelsons, 2008) and improved airway obstruction. A systematic review about the use of airway clearance techniques in patients with COPD found that active airway clearance techniques were effective to remove secretions (Ides et al., 2011). Secondly, the participation in the pulmonary rehabilitation program may have optimized the use of maintenance bronchodilator therapy (Spruit et al., 2013) and it is known that bronchodilators act on airway smooth muscle, reducing air trapping and hyperinflation (O'Donnell et al., 2004; Ramirez-Venegas, Ward, Lentine, & Mahler, 1997). These airway changes might have been responsible for decreasing the flow turbulence, assessed through frequency of normal respiratory sounds, and the genesis of adventitious respiratory sounds (crackles and wheezes). Nevertheless, to confirm the sensitivity to change of computerized respiratory sounds, further clinical research using simple protocols needs to be conducted. Analysis of computerized respiratory sounds before and after an intervention with а known physiological effect, e.g., bronchodilator, bronchochallenge provocation test, cough or active cycle of breathing techniques, constitute possible directions.

Even though only minor changes were found in computerized respiratory sounds after pulmonary rehabilitation, no short- or mid-term changes in FEV<sub>1</sub> were observed (Foglio et al., 2007; Ries, Kaplan, Myers, & Prewitt, 2003). This finding demonstrates that computerized respiratory sounds are a more sensitive indicator on the status of lung function, than FEV<sub>1</sub>. Gavriely et al. (1994) also found that half of patients with a history compatible with COPD had normal spirometry and abnormal respiratory sounds, revealing that airway abnormalities not detectable by standard spirometry generate abnormal acoustic signals (Gavriely, Nissan, Cugell, & Rubin, 1994).

Results from Studies IV and V of this Thesis provide support for considering computerized respiratory sounds as a surrogate outcome measure in COPD. This is especially valuable considering that they can be obtained by integrating computerized techniques with pulmonary auscultation, a quickly, easily and non-invasive method, that is a routine component of patients' physical examination. Nonetheless, future research is needed to strengthen these findings and to extend these observations to other clinical interventions and respiratory diseases.

# Limitations

The findings of this Thesis should be considered in light of a number of limitations.

The first major limitation in this Thesis is the absence of a control group in Studies I and II, where the impact of pulmonary rehabilitation in mild COPD was investigated. Inclusion of a group of patients with mild COPD, with similar sociodemographic and clinical characteristics and receiving standard care, would have strengthened our findings.

Second, outcome assessment was not blinded in Studies I, II and V. The evaluators in these studies were the same physical therapists that delivered the pulmonary rehabilitation programs, which may have influenced the way that outcome measures were assessed. Nonetheless, to minimize bias, the encouragement given by evaluators during all tests was standardized. Further research from blind randomized controlled trials is therefore needed to define the effects of pulmonary rehabilitation in this specific population.

The third main limitation in this Thesis is the cross-sectional design in Study I and the short follow-up periods in Studies II (6 months) and V (3 months), which limit our understanding of (i) the potential of pulmonary rehabilitation to modify the disease trajectory in mild COPD and (ii) the long-term effects of this intervention in computerized respiratory sounds. Although we found positive effects after 12 weeks of pulmonary rehabilitation in patients with mild COPD (Study I) and in computerized respiratory sounds (Study V), it is unclear how long these benefits persist in the absence of continued supervised training. Future work with longer follow-ups is needed to establish the long-term effects of this intervention in patients with mild COPD and in computerized respiratory sounds.

Fourth, the unbalanced sample in terms of COPD severity is another limitation of this Thesis (Studies III, IV and V). Samples were composed mainly of subjects with mild and moderate COPD, and thus, it was not possible to explore how the disease severity related to the reliability (Study III) or sensitivity to change (Studies IV and V) of computerized respiratory sounds. Future studies should use a more balanced sample of COPD grades to clarify these findings and to investigate the computerized respiratory sounds characteristics on each COPD grade.

Fifth, intra-subject reliability of computerized respiratory sounds parameters was explored in patients with COPD (Study III), but not test-retest reliability. This limits the interpretability of our findings, particularly in Studies IV and V, where we assessed the sensitivity to change of computerized respiratory sounds. In addition, Studies IV and V focused on only one parameter per respiratory sound. Future studies could investigate the sensitivity to change of computerized respiratory sounds using other parameters that also have clinical relevance (Marques, Oliveira, & Jácome, 2014). Thus, future work is warranted

to evaluate the psychometric properties of computerized respiratory sounds parameters in patients with COPD.

Lastly, the complex set up used to simultaneously record computerized respiratory sounds and airflow (Studies III, IV and V) restricts the application of computerized respiratory sounds in day-to-day clinical practice. As computerized respiratory sounds shows promise, future research should focus in developing technological solutions to acquire computerized respiratory sounds and airflow with minimal setup.

## Implications for future research and clinical practice

From this Thesis a number of implications for future research and clinical practice can be highlighted.

1. Increase the evidence of pulmonary rehabilitation in mild COPD. This includes further research from blind randomized controlled trials defining its effectiveness and cost-effectiveness in comparison to standard care. Furthermore, it is important to conduct longitudinal studies to explore the potential of this comprehensive intervention to modify the disease trajectory in patients with mild COPD.

2. Increase the access to pulmonary rehabilitation and the sustainable behavior change in mild COPD. This may be achieved through the implementation of community-based pulmonary rehabilitation programs; increasing health professionals and patient awareness of the benefits of pulmonary rehabilitation; and the development of strategies to promote sustainable behavior change.

3. Further understand computerized respiratory sounds in COPD. This includes but is not limited to defining computerized respiratory sounds phenotypes and investigating the genesis of normal and adventitious respiratory sounds. It also comprises the development of technological solutions to acquire computerized respiratory sounds and airflow with minimal setup. 4. Further explore the potential of computerized respiratory sounds as a surrogate outcome measure in COPD. This includes investigating the effect of therapeutic interventions on computerized respiratory sounds in patients with COPD and with other respiratory diseases. In addition, it is important to define the parameters of computerized respiratory sounds with higher sensitivity to change.

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Chapter V

Conclusion

### General conclusion

This Thesis contributes with new evidence on the effectiveness of pulmonary rehabilitation in patients with mild COPD and on the emerging field of computerized respiratory sounds. It has been found that pulmonary rehabilitation has beneficial effects in patients with mild COPD as well as in patients with moderate-to-severe COPD (Studies I and II); and that these effects decline with time (Study II). Computerized respiratory sounds were found to be reliable (Study III) and sensitive to lung function changes due to acute exacerbations of the disease (Study IV) and pulmonary rehabilitation (Study V). Further research should focus on the role of pulmonary rehabilitation in mild COPD trajectory and on the potential of computerized respiratory sounds as a surrogate outcome measure for therapeutic interventions.

Appendices

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Appendix 1. Ethics approval letters

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ai Social 40.204.051 € P	93508 GOIGUVA II' 510 123 210	Ex.ma Senhora Prof.ª Adjunta Alda S Escola Superior de Universidade de Av Campus Universitá 3810-193 Aveiro	ofia Marques Saúde da reiro rio de Santiago
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## AUTORIZAÇÃO N.º 3292 /2013

### I. Do Pedido

A Universidade de Aveiro notificou à CNPD um tratamento de dados pessoais com a finalidade de elaborar um estudo observacional para caraterização e monitorização de sons respiratórios.

O estudo está dividido em três fases:

- Caracterizar os sons pulmonares adventícios em indivíduos saudáveis e em indivíduos com diferentes doenças respiratórias crónicas;
- Implementar programas de reabilitação respiratória em doentes com patologia respiratória; e
- 3) Avaliar os resultados da intervenção a curto, médio e longo prazo.

Serão incluídos na primeira fase do estudo indivíduos saudáveis, recrutados na Universidade de Aveiro e em instituições com protocolo com a universidade, assim como indivíduos com doenças crónicas, que serão convidados a participar pelos hospitais e pelas unidades de cuidados primários que aderirem ao projeto.

Nesta fase, os participantes responderão a vários questionários e será realizado um exame físico, incluindo a recolha computorizada dos sons respiratórios pela equipa de investigação.

Já na segunda fase do estudo, participarão apenas cem indivíduos com doenças respiratórias crónicas, que serão divididos em grupo experimental e grupo de controlo.

A participação nesta fase consiste na implementação de programas de reabilitação respiratória durante doze semanas, compostas por sessões de exercício físico/fisioterapia respiratória e apoio psicoeducativo.

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Por último, a avaliação da intervenção será aferida pela resposta a vários questionários a aplicar antes e após a realização do programa, assim como três, seis e doze meses após o fim do programa.

Os profissionais de saúde assistentes solicitarão consentimento informado aos potenciais participantes no estudo com patologias respiratórias, cuja declaração será conservada em local de acesso reservado na Universidade de Aveiro. Os individuos saudáveis serão recrutados na Universidade de Aveiro e em instituições com protocolos com esta entidade.

Os dados serão recolhidos num caderno de recolha de dados em formato eletrónico, pela equipa de investigação.

No "caderno de recolha de dados" não há identificação nominal do titular, sendo aposto um código de participante. A chave desta codificação só será conhecida da equipa de investigação.

Os destinatários serão ainda informados sobre a natureza facultativa da sua participação e será garantida confidencialidade no tratamento.

### II. Da Análise

A CNPD já se pronunciou na sua Deliberação n.º 227/2007 sobre o enquadramento legal, os fundamentos de legitimidade, os princípios orientadores para o correto cumprimento da Lei n.º 67/98, de 26 de outubro (Lei de Proteção de Dados – LPD), bem como as condições gerais aplicáveis ao tratamento de dados pessoais para esta finalidade.

No caso em apreço, a notificação enquadra-se no âmbito tipificado por aquela Deliberação.

O fundamento de legitimidade é o consentimento expresso do titular dos dados.

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A informação tratada é recolhida de forma lícita (cfr. alínea a) do n.º 1 do artigo 5.º da LPD), para finalidades determinadas, explícitas e legítimas (cfr. alínea b) do mesmo artigo) e não é excessiva.

Alerta-se a responsável pelo tratamento para a necessidade de ser indicado um contacto na declaração de consentimento informado para que, caso os titulares dos dados o desejem, seja exercido o direito de acesso, retificação e oposição, nos termos dos artigos 10.º, 11.º e 12.º da LPD.

#### III. Da Conclusão

Assim, nos termos das disposições conjugadas do n.º 2 do artigo 7.º, n.º 1 do artigo 27.º, alínea a) do n.º 1 do artigo 28.º e artigo 30.º da LPD, com as condições e limites fixados na referida Deliberação n.º 227/2007, que se dão aqui por reproduzidos e que fundamentam esta decisão, autoriza-se o tratamento de dados supra referido, para a elaboração do presente estudo.

Termos do tratamento:

Responsável pelo tratamento: Universidade de Aveiro

Finalidade: Estudo observacional para caraterização e monitorização de sons respiratórios.

Categoria de Dados pessoais tratados:

 na primeira fase do estudo – código de participante, condição de saúde, dados sociodemográficos (mês e ano de nascimento, sexo, habilitações literárias, estado civil e ocupação profissional), dados antropométricos (altura, peso e massa corporal), hábitos tabágicos, comorbilidades, medicação, sintomas respiratórios, número de exacerbações, questionário internacional de atividade física, exame físico, aquisição computorizada dos sons respiratórios;

 na segunda e terceira fases do estudo – código de participante, programa de reabilitação respiratória e avaliação desse programa.

Entidades a quem podem ser comunicados: Não há.

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Formas de exercício do direito de acesso e retificação: Junto da equipa de investigação.

Interconexões de tratamentos: Não há.

Transferências de dados para países terceiros: Não há.

Prazo de conservação: A chave de codificação dos dados deve ser destruída um mês após o fim do estudo.

Dos termos e condições fixados na presente Autorização decorrem obrigações que o responsável deve cumprir. Deve, igualmente, dar conhecimento dessas condições a todos os intervenientes no circuito de informação.

Lisboa, 30 de abril de 2013

Ana Roque (Relatora), Helena Delgado António, Carlos Campos Lobo, Luís Barroso, Luís Paiva de Andrade, Vasco Almeida

Q Phile Filipa Calvão (Presidente)

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Maria, Damas <maria.damas@srsaveiro.min-saude.pt> Enviado: quinta-feira, 2 de Maio de 2013 18:01 Para: Joana Cruz Alda Marques Assunto: RE: Pedido de extensão de autorização ética do ACES BVII para o ACES BV

Exmas. Senhores,

De:

Cc:

Relativamente ao mail infra, informamos V.Exas., que está autorizado o estudo referido, dado que sejam respeitadas as condições do ex ACeS Baixo Vouga II. Melhores Cumprimentos

Maria Augusta Damas

Secretariado ACeS Baixo Vouga E-mail: aces\_bxvouga@srsaveiro.min-saude.pt maria.damas@srsaveiro.min-saude.pt -----Mensagem original-----De: Joana Cruz [mailto:joana.cruz@ua.pt] Enviada: quinta-feira, 2 de Maio de 2013 17:36 Para: Maria, Damas Assunto: FW: Pedido de extensão de autorização ética do ACES BVII para o ACES BV

-----Mensagem original-----De: Alda Marques Enviada: quinta-feira, 11 de Abril de 2013 18:30 Para: dex-aces\_bxvouga@srsaveiro.min-saude.pt; teresa.braz@srsaveiro.min-saude.pt; maria.lamas@srsaveiro.minsaude.pt Cc: Joana Cruz Assunto: Pedido de extensão de autorização ética do ACES BVII para o ACES BV

Ex.mo Sr. Dr. Manuel Sebe,

Na qualidade de investigadora responsável por um projeto de investigação a decorrer no ACES BV II, e necessitando de realizar intervenções em Centros de Saúde que estão abrangidos por todo o ACES do BV, venho por este meio solicitar extensão da autorização ética já concedida previamente. Queira por favor considerar os documentos em anexo para sua análise.

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Melhores cumprimentos, Alda Marques





### DELIBERAÇÃO

Considerando que foram emitidos os devidos esclarecimentos solicitados pela Comissão de Avaliação de Pedidos de Patrocínio Científico e Autorização de Estudos da ARSCentro, I.P., para a realização do projecto "Reabilitar pessoas idosas com DPOC e suas famílias", pela Professora Alda Sofia Pires de Dias Marques e apresentados pelo ACES Baixo Vouga II, o Conselho Directivo decide autorizar a sua realização nos termos solicitados.

Coimbra, 28 de Fevereiro de 2011

**O** Conselho Directivo da Administração Regional de Saúde do Centro, IP (Dr. João Pedro Pimentel) Presidente Receiver (Dr. Mário Rui Ferreira) Vice-Presidente Ŀ re tu 00 oaquím Gomes da Silva) Dr. Vogal  $\cap$ (Dr.ª Regina Dias Bento) Vogal

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Appendix 2. Consent forms

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## Termo de Consentimento Livre e Esclarecido

**Título do Projeto:** Sons respiratórios computorizados em pessoas com Doença Pulmonar Obstrutiva Crónica

Nome do investigador principal: Alda Marques

## Por favor leia e assinale com uma cruz (X) os quadrados seguintes.

1. Eu confirmo que percebi a informação que me foi dada e tive a oportunidade de questionar e de me esclarecer.

2. Eu percebo que a minha participação é voluntária e que sou livre de desistir, em qualquer altura, sem dar nenhuma explicação, sem que isso afecte qualquer serviço de saúde que me é prestado.

3. Eu compreendo que os dados recolhidos durante a investigação são confidenciais e que só os investigadores do projecto da Universidade de Aveiro têm acesso a eles. Portanto, dou autorização para que os mesmos tenham acesso a esses dados.

4. Eu compreendo que os resultados do estudo podem ser publicados em Revistas Científicas e usados noutras investigações, sem que haja qualquer quebra de confidencialidade. Portanto, dou autorização para a utilização dos dados para esses fins.

5. Eu concordo então em participar no estudo.

Nome do participante	Data	Assinatura
Nome do Investigador(a)	Data	Assinatura

Sons respiratórios computorizados em pessoas com Doença Pulmonar obstrutiva Crónica (SFRH/BD/84665/2012)

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# Termo de Consentimento Livre e Esclarecido

Título do Projeto: Reabilitar pessoas com Doença Pulmonar Obstrutiva Crónica Nome do investigador principal: Alda Marques

Por favor leia e assinale com uma cruz (X) os quadrados seguintes.

1. Eu confirmo que percebi a informação que me foi dada e tive a oportunidade de questionar e de me esclarecer.

2. Eu percebo que a minha participação no programa de reabilitação respiratória é voluntária e que sou livre de desistir, em qualquer altura, sem dar nenhuma explicação, sem que isso afete qualquer serviço de saúde que me é prestado.

3. Eu concordo que as sessões do programa de reabilitação respiratória sejam filmadas com o objetivo de ajudar no planeamento de futuros programas de reabilitação respiratória.

4. Eu compreendo que os dados recolhidos durante a investigação são confidenciais e que só os investigadores do projeto da Universidade de Aveiro têm acesso a eles. Portanto, dou autorização para que os mesmos tenham acesso a esses dados.

5. Eu compreendo que os resultados do estudo podem ser publicados em Revistas Científicas e usados noutras investigações, sem que haja qualquer quebra de confidencialidade. Portanto, dou autorização para a utilização dos dados para esses fins.

6. Eu concordo então em participar no estudo.

Nome da pessoa	Data	Assinatura
Nome do Investigador(a)	Data	Assinatura

Reabilitar pessoas com Doença Pulmonar Obstrutiva Crónica (SFRH/BD/84665/2012)