



**Chronic Obstructive Pulmonary Disease: health status, activities of daily living,
resistance training and exacerbation**

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*Ensinar não é transferir conhecimento, mas criar as possibilidades para a sua própria
produção ou a sua construção.*

Paulo Freire

Resumo

Introdução: Pacientes com DPOC podem apresentar um estilo de vida fisicamente inativo e sedentário, entrando no ciclo vicioso da inatividade e descondicionamento, levando à redução na capacidade funcional, que associado à dispneia leva limitações nas atividades de vida diária (AVD). O treinamento físico é um dos pilares no tratamento da DPOC e apesar de todas as evidências descrevendo os benefícios do treinamento resistido ainda não é consensual o entendimento relacionado à intensidade do treinamento resistido e seus benefícios. Além disso, episódios de exacerbações são frequentes em pacientes com DPOC e repetidas exacerbações possuem uma profunda influência no estado de saúde, incluindo impactos na qualidade de vida e estado funcional. Essas questões foram o aspecto central desta tese. **Objetivos:** avaliar as limitações durante AVD e verificar se a escala *London Chest Activity of Daily Living* (LCADL) e o questionário *Saint George's Respiratory Questionnaire* (SGRQ) são capazes de refletir as limitações nas AVD. Investigar o desempenho e dispneia nas AVD, capacidade de exercício e qualidade de vida após 36 sessões de diferentes intensidades de treinamento resistido. Sintetizar as evidências existentes sobre o impacto da exacerbação da DPOC no estado de saúde.

Métodos: foi realizado um estudo observacional que avaliou 48 pacientes com DPOC pelo LCADL, SGRQ e por uma simulação de AVD; um estudo clínico randomizado com grupos paralelos, que avaliou as limitações nas AVD, capacidade funcional, queixas e qualidade de vida antes e após 36 sessões de exercício resistido - n=13: baixa-carga/alta-repetição (LL/HR) e n=11: alta-carga/baixa-repetição (HL/LR) - combinado ao aeróbio; e uma revisão sistemática realizada no PubMed. **Resultados:** correlação positiva e moderada foi encontrada entre LCADL e SGRQ e dispneia e demanda metabólica nas AVD. A dispneia na ADL3 e a demanda metabólica na ADL1 explicaram 33% da variabilidade em LCADL%. A dispneia e a demanda metabólica na ADL3 explicaram 67% da variabilidade no SGRQ. Houve redução da dispneia nas AVD e LCADL, aumento da capacidade de exercício e força muscular após ambas intensidades de treino resistido. Uma interação entre a intervenção e o tempo foi observada no domínio dos sintomas do SGRQ com efeito do tempo no grupo LL/HR. Baseado em 16 artigos foi possível sintetizar as evidências sobre o impacto das exacerbações no estado de saúde, destes seis estudos avaliaram o efeito de uma única exacerbação enquanto 12 estudos avaliaram a influência da exacerbação ou da frequência de exacerbação nas mudanças no estado de saúde ao longo do tempo. **Conclusão:** a escala LCADL refletiu 33% e o questionário SGRQ refletiu 67% da limitação funcional – dispneia e demanda metabólica - durante uma simulação de AVD. Houve um efeito superior do treino de LL/HR sobre o domínio sintomas do SGRQ. Por fim, verificou que existe um impacto prejudicial a curto e longo prazo das exacerbações sobre os sintomas relacionados às AVD e qualidade de vida. Os impactos a longo prazo de (repetidas) exacerbações sobre a tolerância ao exercício, força muscular e níveis de atividade física é menos estudado e/ou existem evidências conflitantes.

Abstract

Background: Patients with COPD might present a physically inactive and a sedentary lifestyle, so they start a vicious circle of inactivity and deconditioning, which also causes a decrease in functional capacity. The onset of dyspnea and fatigue and disease progression leads to impairments in activities of daily living (ADL). The exercise training appears being one of the cornerstone in treatments of COPD. Despite of all evidences describing the benefits of resistance training, still unclear and understanding regarding the comparison between different intensities of resistance training. Furthermore, exacerbations are frequent in patients and repeated exacerbations have a profound influence on health status. These issues were the central aspect of this thesis. **Objectives:** to assess the limitation during ADL and whether London Chest Activity of Daily Living (LCADL) and Saint George's Respiratory Questionnaire are able to reflect the real ADL limitation. To investigate ADL performance and dyspnea, exercise capacity and quality of life after 36 sessions of two different resistance training intensities. To summarize the existing evidence on the impact of exacerbation of COPD on health status. **Methods:** a cross-sectional study which assessed 48 COPD patients by SGRQ and LCADL and an ADL simulation was performed; a randomized parallel-group trial was performed, which one assessed ADL limitation, functional capacity, complaints and quality of life before and after 36 sessions of resistance training - n= 13: low-load/high repetition (LL/HR) and n=11: high-load/low-repetition (HL/LR) - combined with aerobic training. A systematic review was performed on PubMed from inception until September 2017. **Results:** LCADL_% and SGRQ showed a moderate positive correlation with dyspnea and metabolic demand during ADL. The dyspnea in ADL3 and metabolic demand in ADL1 explained 33% of the variability in LCADL_%. The dyspnea and metabolic demand in ADL3 explained 67% of the variability in SGRQ. Both intensities improved in the same magnitude dyspnea during ADL and LCADL, in exercise capacity, muscle strength. An interaction between intervention and time was observed in symptom domain of SGRQ with greater effect of time in LL/HR group. Based in 16 articles of which six studies assessed the direct effect of a single exacerbation on health status while 12 studies assessed the influence of exacerbation occurrence or exacerbation frequency on longitudinal changes over time. **Conclusion:** LCADL reflects 33% and SGRQ reflects 67% of the functional limitation during ADL simulation, such as dyspnea and the metabolic demand during ADL. There was a superior effect of LL/HR training in symptoms domain of SGRQ. Regarding the impact of exacerbations of COPD on health status, detrimental short- and/or long-term impact on symptoms related to activities of daily life and health-related quality of life was clearly revealed. The long-term impact of (repeated) exacerbations on exercise tolerance, muscle strength and physical activity levels is less studied and/or conflicting evidence is existing.

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Prefácio

Essa tese será apresentada como parte dos requisitos para a obtenção do título de Doutora em Fisioterapia pela Universidade Federal de São Carlos – UFSCar, Brasil e em Ciência da Reabilitação em Fisioterapia pela Universidade de Hasselt, Bélgica.

Um acordo de cooperação foi firmado entre as duas universidades, e para gozar do título de Doutora por ambas as universidades, a tese será redigida em língua inglesa.

O capítulo 1 abrange uma introdução que compreende a fundamentação teórica e justificativa para a realização dos estudos que compreendem essa tese.

Os artigos descritos nos capítulos 2 e 3 foram conduzidos sob a supervisão da Professora Doutora Valéria Amorim Pires Di Lorenzo, no Laboratório de Espirometria e Fisioterapia Respiratória (LEFiR) da UFSCar.

O manuscrito apresentado no capítulo 2 intitulado “*Do London Chest Activity Daily Living Scale and Saint George's Respiratory Questionnaire reflect real limitations during activities of daily living in patients with COPD?*” foi aceito para publicação no *Journal of Cardiopulmonary Rehabilitation and Prevention* (número do manuscrito: JCRP-D-17-00078R). Esse estudo teve como objetivo avaliar as limitações durante atividades de vida diária (AVD) em 48 pacientes e se a escala *London Chest Activity of Daily Living (LCADL)* e o questionário *Saint George's Respiratory Questionnaire (SGRQ)* são capazes de refletir as reais limitações durante a simulação de AVD.

O capítulo 3 é composto pelo ensaio clínico randomizado intitulado “*Different intensities of resistance training and the impact on health status focusing on activities of daily living in patients with COPD: a randomized controlled parallel study*” o qual foi submetido para a publicação no periódico *Clinical Rehabilitation* e teve como objetivo investigar o desempenho nas AVD bem como dispneia, capacidade de exercício e qualidade de vida após 36 sessões de dois exercícios resistidos, os quais se diferem pela intensidade.

A revisão sistemática descrita no capítulo 4 foi conduzida sob a supervisão do Professor Dr. Marjin Spruit a co-supervisão do Professor Dr. Chris Burtin no Centro de Pesquisa em Reabilitação, grupo de pesquisa em Doenças Cardiorrespiratória e Internas da Universidade de Hasselt, Diepenbeek, Bélgica. Essa revisão teve como objetivo sintetizar de forma sistemática as evidências encontradas na literatura a respeito do impacto de um episódio

de exacerbação bem como repetidas exacerbações ao longo do tempo sobre o estado de saúde de pacientes com DPOC.

No capítulo 5 o leitor encontrará as considerações finais referente aos achados dos três artigos apresentados anteriormente bem com suas implicações clínicas.

Parte dos trabalhos constituintes dessa tese já foram publicados em forma de resumos em alguns dos mais importantes congressos mundiais:

Barusso-Grüninger, M; Gianjeppe-Santos J; Di Lorenzo VAP. Impact of metabolic and ventilatory demand during activities of daily living on oxygen saturation and dyspnea. In: European Respiratory Society International Congress, 2017, Milan. European Respiratory Journal 2017 50: PA2516; DOI: 10.1183/1393003.congress-2017.PA2516.

Barusso MS; Gianjeppe-Santos J; Sentanin AC; Di Lorenzo VAP. Escala London e questionário Saint George refletem reais limitações nas AVD de pacientes com DPOC?. In: XVIII Simpósio Internacional de Fisioterapia Cardiorrespiratória e Fisioterapia em Terapia Intensiva, 2016, Belo Horizonte. ASSOBRAFIR Ciência. Londrina: ASSOBRAFIR Ciência, 2016. v. 7. p. 323-324.

Gianjeppe-Santos J; Barusso MS; Sentanin AC; Panin JC; Di Lorenzo VAP. Responsiveness of dyspnea, impact of COPD on health status and quality of life on aerobic and resistance training in different intensities? Pilot study. In: European Respiratory Society International Congress, 2015, Amsterdam. European Respiratory Journal, 2015. v. 46.

Barusso MS; Gianjeppe-Santos J ; Regueiro EMG ; Panin JC; Di Lorenzo VAP. Impact of aerobic and resistance training of different intensities on peripheral muscle strength and BODE index in patients with COPD - pilot study. In: European Respiratory Society International Congress, 2014, Munich. European Respiratory Society, 2014.

Preface

This thesis is submitted for a joint PhD degree in Physiotherapy at Federal University of São Carlos – UFSCar, Brazil and in Rehabilitation Sciences and Physiotherapy at Hasselt University - UHasselt, Belgium.

A cooperation agreement was signed between the two universities, and in order to enjoy the PhD from both universities, the thesis will be written in English.

The Chapter 1 encompass a theoretical introduction to the field of research with justification for carrying out the studies.

The manuscripts described in Chapter 2 and 3 was conducted under the supervision of Professor Valéria Amorim Pires Di Lorenzo in Spirometry and Respiratory Physiotherapy Laboratory (LEFIR) from UFSCar.

The manuscript from Chapter 2 titled “Do London Chest Activity Daily Living Scale and Saint George's Respiratory Questionnaire reflect real limitations during activities of daily living in patients with COPD?” has been accepted to publication in Journal of Cardiopulmonary Rehabilitation and Prevention (manuscript number: JCRP-D-17-00078R). This study assessed the limitation during activities of daily living (ADL) in 48 COPD patients and whether LCADL and SGRQ are able to reflect the real ADL limitations.

Chapter 3 addresses a randomized trial titled “Different intensities of resistance training and the impact in health status focusing on activities of daily living in patients with COPD: a randomized controlled parallel study” has been submitted to Clinical Rehabilitation. This study had the aim to investigate ADL performance and dyspnea, exercise capacity and quality of life after 36 sessions of two different resistance training intensities.

The systematic review described in Chapter 4 was conducted under supervision of Professor Martjin Spruit and co-supervision of Professor Chris Burtin in the Rehabilitation Research Center, Cluster Cardiorespiratory and Internal disorders from Hasselt University (UHasselt), Belgium. This review aims to summarize existing evidence on the impact of exacerbation of COPD on health status.

In Chapter 5, the reader will find the final considerations based in the findings of the three previously manuscripts and the clinical implications of the findings.

Part of this work has been presented in the following abstracts published in some one of the most important worldwide congress:

Barusso-Grüninger, M; Gianjeppe-Santos J; Di Lorenzo VAP. Impact of metabolic and ventilatory demand during activities of daily living on oxygen saturation and dyspnea. In: European Respiratory Society International Congress, 2017, Milan. European Respiratory Journal 2017 50: PA2516; DOI: 10.1183/1393003.congress-2017.PA2516.

Barusso MS; Gianjeppe-Santos J; Sentanin AC; Di Lorenzo VAP. Escala London e questionário Saint George refletem reais limitações nas AVD de pacientes com DPOC?. In: XVIII Simpósio Internacional de Fisioterapia Cardiorrespiratória e Fisioterapia em Terapia Intensiva, 2016, Belo Horizonte. ASSOBRAFIR Ciência. Londrina: ASSOBRAFIR Ciência, 2016. v. 7. p. 323-324.

Gianjeppe-Santos J; Barusso MS; Sentanin AC; Panin JC; Di Lorenzo VAP. Responsiveness of dyspnea, impact of COPD on health status and quality of life on aerobic and resistance training in different intensities? Pilot study. In: European Respiratory Society International Congress, 2015, Amsterdam. European Respiratory Journal, 2015. v. 46.

Barusso MS; Gianjeppe-Santos J; Rigueiro EMG ; Panin JC; Di Lorenzo VAP. Impact of aerobic and resistance training of different intensities on peripheral muscle strength and BODE index in patients with COPD - pilot study. In: European Respiratory Society International Congress, 2014, Munich. European Respiratory Society, 2014.

Chapter 1

Introduction to the field of research

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality and studies on the burden of the disease estimate that by 2030, it will be the fourth major cause of death in the world^{1,2}.

According to the Global Initiative for Chronic Obstructive Lung Disease – GOLD², COPD is a common, preventable and treatable disease, characterized by a persistent respiratory symptoms and airflow obstruction. It is associated airway and/or alveolar abnormalities due to the inhalation of noxious gases and particles. Furthermore, COPD patients may present chronic respiratory symptoms - as cough, sputum production, and shortness of breath – as well as activity limitation prior the development of airflow limitations and it has been associated with acute respiratory events – exacerbation³.

Beyond the lungs, it is clearly established that COPD patients present low-grade systemic inflammation and it has been implicated in the pathogenesis of the majority of the systemic effects of COPD, as weight loss, oxidative stress, skeletal muscle dysfunction, cardiovascular disease, depression, and osteoporosis⁴⁻⁷ (Figure 1).

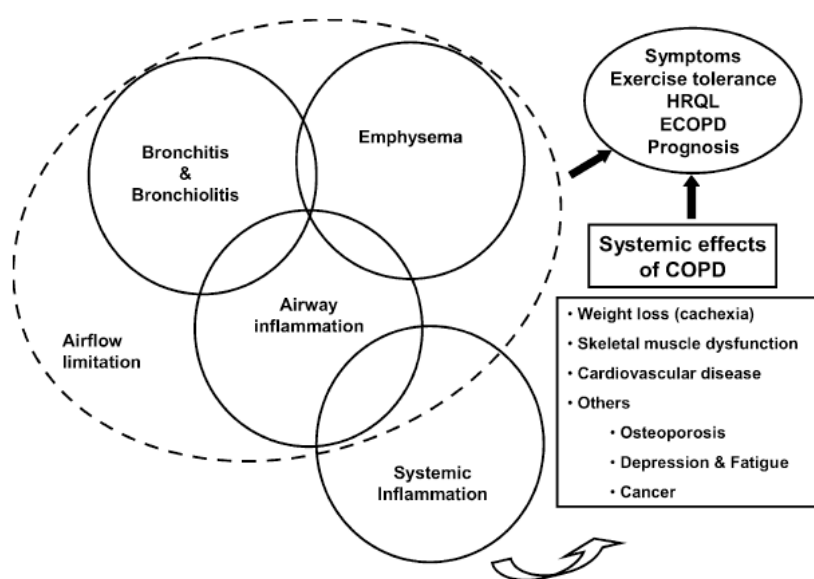


Figure 1. Chronic obstructive pulmonary disease (COPD) can be considered to have several domains, both inside and outside the lungs, that contribute to the physiologic (airflow obstruction) and clinical characteristics of patients. Abbreviations: ECOPD= exacerbation of COPD; HRQL= health-related quality of life⁸.

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Patients might present a physically inactive and a sedentary lifestyle, so they start a vicious circle of inactivity and deconditioning⁹, which also causes a decrease in functional capacity along with muscle dysfunction due to disuse.

Limb muscle dysfunction - defined as weakness, reduced endurance, or greater fatigability which reflect both structural and metabolic muscle adaptations¹⁰ - is often observed in patients with COPD and contributes, independent of lung function impairment, to important

outcomes such as increased mortality, greater healthcare utilization, and poor health status¹⁰⁻¹³. Muscle weakness is heterogeneously distributed among muscle groups. The strength of upper limbs is better preserved than lower limbs, although muscle weakness can also be found in the upper extremities¹⁰. Indeed, patients with COPD stop exercising primarily due to leg fatigue complaints, affecting exercise capacity and subsequently leading to difficulties in performing activities of daily living (ADL).

Functional exercise capacity impairment has consistently been associated with poor outcomes such as higher risks of respiratory and all-cause mortality in patients with COPD and field walking tests play a key role in its evaluation¹⁴. The worsening of functional capacity has been described as a tough challenge for patients and their families¹⁵. Therefore, accurately assessing functional status becomes important, being the 6-minute walk test (6MWT) one of the most widely used assessments tool of functional exercise capacity in this population. The distance covered during the test, the 6-minute walk distance (6MWD) is considered the primary test outcome¹⁶. Furthermore, 6MWD was consistently associated with symptoms, health-related quality of life (HRQoL) and objective measures of physical activity in patients with COPD¹⁴.

The onset of dyspnea and fatigue, as well as disease progression lead to impairments in ADL which are described as activities related to subjects' routine, as self-care, domestic task and leisure. These are simple but essential activities to the patient's independence, as they allow them to carry out activities at home¹⁷. Both basic ADL - those required for daily life, such as eating, dressing, bathing – and instrumental ADL – those required for adapting independently to the environment¹⁸, such as preparing meals, house maintenance, and all other leisure activities - are also impaired by dyspnea.

Taking into account that most of the ADL needs a great range of upper limb movements with different degrees of chest muscle involvement, also recruiting the accessory respiratory muscles to sustain the movement. Besides that, ADL involving trunk flexion, such as making the bed and putting on shoes subjects has a rapid, shallow, and irregular breathing pattern¹⁹, and even oxygen desaturation²⁰.

Progressively, patients decrease the ability to perform ADL, presenting limitations in activities which were previously performed without limitation²¹, such as increase in dyspnea and oxygen desaturation²⁰. Furthermore, oxygen desaturation may occur during these activities due to imbalance between oxygen supply and demand, which can be attributed

to ventilatory, hemodynamic, and/or peripheral muscle disorders, or a combination of these²². Besides that, patients with COPD can achieve 55% of maximal oxygen consumption and 60-70% maximal voluntary ventilation during ADL performance, with a consequent decrease in metabolic and ventilatory reserves²³.

Velloso and colleagues²³ showed that patients with COPD present high oxygen consumption (VO_2) when performing four pre-selected ADL, which could explain the fatigue during the performance of ADL. Furthermore, the high ventilatory demand could be related also to dyspnea. Jeng and colleagues²⁴ found greater dyspnea during the performance of ADL when compared COPD patients with healthy individuals. Vaes and colleagues²⁵ found that COPD patients use a high proportion of aerobic capacity and ventilation with higher reported dyspnea during ADL compared to healthy elderly individuals. Therefore, assessing the limitations of ADL is important, since these can be used as a predictor of mortality²⁶ and have an important role in the quality of life of COPD patients²⁷.

The simplest methods to assess ADL performance are questionnaires and scales, which are accessible tools. Through reports from patients it is possible to establish the difficulties in performing ADL. Among the scales, the modified Medical Research Council (mMRC)²⁸ dyspnea and scale London Chest Activity of Daily Living (LCADL)²⁹ has been widely used to assess the impact of dyspnea during ADL in COPD patients, as these are disease-specific.

The mMRC scale is a 5-item scale in which patient needs to choose which one better reflects patients' dyspnea perception during ADL. Higher punctuation means greater limitation due to dyspnea in ADL^{28,30}. The LCADL scale consists of four domains: self-care, domestic, physical, and leisure. In those 4-domains, this scale encompasses 15 quantitative questions, with a higher number of ADL such as dressing-up, washing hair, making beds, changing sheet, walking upstairs, bending, going out socially etc. Subjects indicate a score of 0-5 for each activity, with the largest value representative of maximum inability to perform ADL due dyspnea²⁹.

Both scales assess dyspnea during ADL based on patient's perception of past events, and as described in a previous study from our research group²⁰, even fewer symptomatic patients - assessed by questionnaires and scales - showed significant dyspnea and oxygen desaturation during ADL.

Activities of daily living performance-based protocols could be a more realistic way to assess the limitation during these activities, providing us additional information than that obtained through the questionnaires³¹. A systematic review³¹ described that a few multitask protocols have been developed to assess ADL performance in patients with COPD, but it still unknown whether ADL performance based on performance-based protocol reflects the ADL impairment assessed by self-reported tools.

Furthermore, the association of decline in exercise capacity and impairments in ADL performance are commonly associated with decrease in HHQoL, which is usually defined as an individual's perception of the position in life or life satisfaction. The evaluation of HRQoL has become an important outcome measure in COPD research and treatment³² and it is commonly assessed by the Saint George's Respiratory Questionnaire (SGRQ), which is a disease-specific questionnaire and approaches aspects related to three domains: symptoms – related to discomfort caused by respiratory symptoms, activity – related to changes in physical activity, and impact – assess the overall impact on ADL and patient well-being³³. Indeed, limitation in ADL reflects in reduction in HRQoL, therefore the relation between the real limitation during ADL and HRQoL needs to be better understanding.

The concepts of quality of life, HRQoL, functional impairment, and symptoms are often used interchangeably³⁴⁻³⁸. Current theories on health status are rather abstract and do not define the health status on the level of possible underlying sub-domains³⁹. Furthermore, many health status instruments were used for different purposes, including performance-driven and patient-reported measures³⁴⁻³⁷.

In this way, Vercoulen and colleagues (2008)³⁹ suggested that the sub-classification of health status in patients with COPD encompasses distinct main domains of health status: physiological functioning, complaints, functional impairment and quality of life. These sub-domains classification allows a more concrete and detailed definition of health status, whereas the sub-domains of health status are relatively independent. Therefore, the integral assessment is essential for tailoring interventions to the needs of each patient³⁹.

Counteracting all the limitations described above, exercise training appears is the cornerstone in non-pharmacological treatments for COPD⁴⁰. Important goals of exercises interventions are not limited to improvements in muscle strength and endurance, and aerobic capacity, but also meaningful changes in functional performance. Changes in daily living

activities and improvements in quality of life have been highlighted in the rehabilitation field⁴⁰⁻⁴².

Concerning resistance training, the vast majority of studies focus on increases in muscle strength, working with a high load and low or moderate number of repetitions, as it is known that muscle weakness is a common problem in COPD patients, and resistance exercise can lead to appreciable increases in arm and leg muscle strength in this population⁴³. Furthermore, improving limb muscle endurance in patients with COPD has been highlighted as an important therapeutic goal⁴⁴, since muscle endurance seems to be more closely related to functionality than muscle strength in these patients¹².

A review by O'Shea⁴³ reported a large effect favoring progressive resistance exercise in tests reflecting ADL, such as stair-climbing performance and the sit-to-stand test, however the vast majority of studies included in this review started the training with high-load resistance training and the trials compared either progressive resistance exercise with no intervention, or with combined aerobic and resistance training, or compared with aerobic training alone.

There is no clear and consensual the understanding regarding the comparison between different intensities of resistance training and the improvements in ADL performance, dyspnea, and health status in COPD patients, which needs to be better understood.

Furthermore, COPD is characterized by the onset of exacerbations, which are defined as an acute worsening of respiratory symptoms that results in additional therapy⁴⁵. Severe exacerbations often require hospitalization and are associated with increased dyspnea symptoms which usually last for seven to ten days, but might be present for weeks to months in some patients^{45,46}. Exacerbations are not random events but cluster together in time; there is a high-risk period of eight weeks after the exacerbation during which time a new exacerbation may be experienced⁴⁷. In light of this, the strongest predictor of experiencing an exacerbation is the number of exacerbations in the past year⁴⁸. The frequency of severe exacerbations is associated with a faster lung function decline⁴⁹ and increased mortality risk⁵⁰.

Moreover, literature suggests that (repeated) exacerbations have a profound influence on health status beyond the lungs including quality of life and functional status. The onset of deconditioning and muscle dysfunction has been suggested to have a role in this. Patients with frequent exacerbations may be at risk of becoming frail and inactive, which increases the likelihood to experience new exacerbations and to die^{51,52}. A summarization of

the existing evidence on the impact of exacerbation of COPD on health status beyond pulmonary function in a systematic manner needs to be done.

Based in all the findings mentioned above, the three manuscripts that give rise to the present thesis are done:

- Manuscript number 1: “Do London Chest Activity Daily Living Scale and Saint George's Respiratory Questionnaire reflect real limitations during activities of daily living in patients with COPD?”.

- Manuscript number 2: “Different intensities of resistance training and the impact on health status focusing on activities of daily living in patients with COPD: a randomized controlled parallel study”

- Manuscript number 3: “Short and long-term effects of acute exacerbations on health status beyond pulmonary function in patients with COPD - a systematic review.”

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Chapter 2

Do London Chest Activity Daily Living Scale and Saint George's Respiratory Questionnaire reflect real limitations during activities of daily living in patients with COPD?

In this chapter we will describe the aim, methods, results and discussion from the manuscript titled Do London Chest Activity Daily Living Scale and Saint George's Respiratory Questionnaire reflect real limitations during activities of daily living in patients with COPD?

This manuscript has been accepted to publication in Journal of Cardiopulmonary Rehabilitation and Prevention (manuscript number: JCRP-D-17-00078R).

The hypothesis of the present study is that London Chest Activity Daily Living Scale (LCADL) and Saint George's Respiratory Questionnaire (SGRQ) are able to reflect the patient's real limitation during activities of daily living (ADL). The aims of the present study were to assess the peripheral oxygen saturation (SpO_2), SpO_2 variation (ΔSpO_2), dyspnea, metabolic and ventilatory demand during ADL simulation; to identify whether the LCADL and SGRQ are able to reflect the patient's real limitations during ADL simulation.

Methods

Study design and Subjects

This is an observational, cross-sectional study developed in the Laboratory of Spirometry and Respiratory Physiotherapy of the Federal University of São Carlos, São Paulo, Brazil, from October 2013 to January 2016, approved by the Human Research Ethics Committee (0354.0.135.000-11).

Inclusion criteria were: patients with a confirmed diagnosis of moderate to severe COPD¹; aged 60 years or over; both genders; and no change in medication and clinical stability for at least 2 months. Exclusion criteria were: severe heart disease; myocardial ischemia; musculoskeletal/orthopedic condition that limited exercise; uncontrolled systemic hypertension; participation in pulmonary rehabilitation program within previous 6-months; exacerbation of clinical symptoms during the study and incomplete assessment. After the assessment, all patients were referred for a pulmonary rehabilitation program (NCT01977469).

Protocol

The protocol consisted of 3 non-consecutive days with a 48-h interval between assessments. On the first day data related to sample characterization were collected: the history, comorbidities (Charlson index), and disease impact on health status (COPD Assessment test). In addition, the mMRC, LCADL, and SGRQ were applied and the 6-minute walk test (6MWT) performed. On the second day, a symptom-limited cardiopulmonary exercise test (CPET) was

performed. On the third day, the ADL assessment was performed associated with gas analysis. All scales and questionnaires were applied as an interview in a quiet environment, always by the same examiner.

The SGRQ approaches aspects related to three domains which address aspects of respiratory symptoms, changes in physical activity, and the overall impact on ADL and patient well-being. Higher scores are related to poorer quality of life^{2,3}.

The LCADL assesses limitations to perform ADL due to dyspnea⁴ and a higher total score indicates greater limitation in performing ADL due to dyspnea. It is composed of four domains: self-care, domestic activities, physical activities, and leisure. A total score⁴ and percentage of total were calculated. LCALD% calculation is described in our previously study⁵. Both SGRQ^{2,3} and LCADL⁶ were translated and validated for the Brazilian population.

The 6MWT was performed according to the standards of the European Respiratory Society and American Thoracic Society⁷. Two tests were performed with a 30-minute interval between attempts and the longest distance was considered for the statistical analyses, in addition, a percentage of predicted was determined⁸.

To determine peak of oxygen consumption (VO_{2peak}) a symptom limited CPET was performed for subsequent calculation of the metabolic demand during ADL. The test was performed on a cycle ergometer, and the gas samples were collected via a metabolic system (VO2000 System; MedGraphics), by an average of three breaths. The test began with a 3-minute rest followed by a 1-minute warm-up with subsequent load increases of 5 watts each 2 minute, maintaining a pedaling cadence between 50-60 rpm. The criterion for interrupting the test was according to the American Thoracic Society/American College of Chest Physicians⁹.

ADL Assessment

ADL simulation was carried out as described by a previous study⁵. Three ADL were performed by patients: showering simulation (ADL1), lifting and lowering containers from a shelf above the shoulder girdle (ADL2), and raising and lowering pots on a shelf below the pelvic girdle (ADL3). All chosen ADL involved trunk flexion and rotation and unsupported upper limb movements; being capable of leading to greater increases in ventilation and oxygen consumption^{10,11}.

The activities were all accompanied by the same evaluator, and patients were instructed to perform them in the aforementioned order, as a circuit, and as performed at home, with no time limit for their execution.



Figure 1. COPD patient performing activities of daily living. **Legend:** ADL1: taking shower; ADL2: containers above scapular girdle; ADL3: pots below pelvic girdle.

Ventilation (VE), oxygen consumption (VO_2), and metabolic equivalent (MET) were collected during ADL, using the same metabolic system as the CPET. Maximal voluntary ventilation (MVV) was obtained by the equation $FEV_1 * 37.5^{12}$.

Ventilatory (VE_{ADL}/MVV) and metabolic (VO_{2ADL}/VO_{2peak}) demand were subsequently calculated. Values above 60% were considered as high metabolic and ventilatory demands¹³. Furthermore, heart rate (HR), SpO_2 , dyspnea, and fatigue were analyzed at rest and immediately after each ADL.

ΔSpO_2 was calculated at the end of each ADL using the equation: $\Delta SpO_2 = SpO_{2ADL} - SpO_{2rest}$. Oxygen desaturation was taken as values below 88%¹⁴ and/or $\Delta SpO_2 \geq 4\%$ ¹⁵.

Statistical Analysis

Data were analyzed using Statistical Package of Social Sciences (SPSS, v.23.0). Shapiro-Wilk test was used to assess data normality. All variables were described as mean (standard deviation).

Repeated measures ANOVA was applied to compare the metabolic and ventilatory variables at the end of each ADL and its non-parametric equivalent.

Correlation coefficients were used to identify correlations between LCADL and SGRQ and the outcomes: ΔSpO_2 , dyspnea, fatigue, and metabolic and ventilatory demand. The

correlation coefficients were classified by strength according to Bryman and Cramer: weak (r-value: 0.2-0.39); moderate (r-value: 0.4-0.69), and strong correlations (r-value: 0.7-0.89).

Finally, a stepwise multiple linear regression was applied using $\text{LCADL}_{\%total}$ and SGRQ as the dependent variables and the variables with a moderate correlation as independent variables. The significance level for the statistical analysis was set at 5% ($p < 0.05$).

The sample size was calculated to achieve a correlation of at least 0.4 between the LCADL and SGRQ and the outcomes: ΔSpO_2 , dyspnea, fatigue, and metabolic and ventilatory demands during ADL. With a bidirectional α of 0.05 and $\beta = 0.20$, the estimated sample size was 47 subjects¹⁶.

Results

Clinical characteristics of patients

Forty-eight patients were included in the study (Figure 2). Twenty-three (47.9%) were classified as moderate COPD, 22 (45.8%) as severe, and three (6.3%) as very-severe, according to the GOLD classification¹ based on FEV_1 . The clinical characteristics of them are described in table 1.

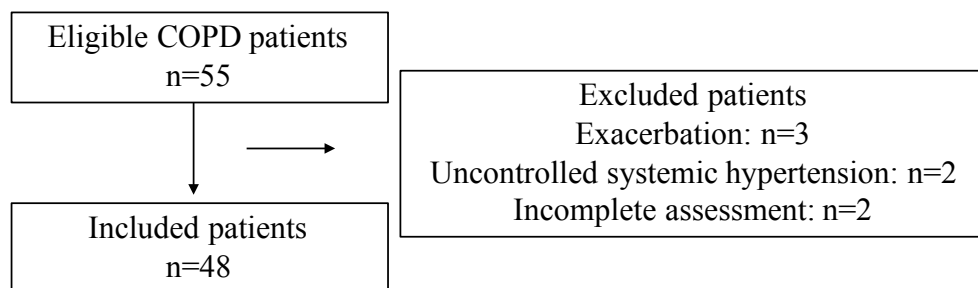


Figure 2. Flow chart of inclusion and exclusion of subjects in the study.

Table 1. Anthropometric and clinical data of the sample, 6MWT and mMRC, CAT, SGRQ and LCADL scores

	COPD (n=48)
Gender, n	7F 41M
Age, y	69.57±8.22
Smoking history. pack-years	75.35±60.61
Charlson comorbidity index	1.33 ± 0.59
BMI, kg/m ²	24.59±4.84
FEV ₁ , L	1.37±0.49
FEV ₁ , % predicted	50±13
mMRC	1.73 ±0.96
CAT score	13.26±6.90
SGRQ, %	
Symptoms	36.9±21
Activities	53.59±21.58
Impact	27.92±7.34
Total	36.4±17.76
LCADL scale	
Self-care	5±1
Domestic	4±3
Physical	3±1
Leisure	3±0
Total	16±4
Total, %	28.08±8.44
6MWD, m	403± 96
6MWD, % predicted	79.56±17.68
CPET VO _{2peak} , l	0.88±0.21
CPET VO _{2peak} , ml.kg.min ⁻¹	13.01±3.85

Values expressed as mean ± standard deviation, median (interquartile range) or number of subjects. **Legend:** **F**=female; **M**=male; **BMI**=body mass index; **FEV₁**=forced expiratory volume in first second; **mMRC**= *Modified Medical Research Council*; **CAT**=COPD Assessment Test; **SGRQ**=Saint George Respiratory Questionnaire; **LCADL**=London Chest Activity of Daily Living; **6MWD**= 6-minute walk distance.

Comparison of ventilatory and metabolic variables between ADL

The time spent to perform all ADL was 875 ± 190 seconds. SpO₂ and ΔSpO₂ in ADL2 were statistically lower compared to ADL3. In addition, the percentage of patients who presented oxygen desaturation in ADL1 (41.7%) was higher compared to ADL2 (33.3%), and ADL3 (25%) as well as having a higher percentage of these patients in ADL2 compared to ADL3 (Table 2).

HR, VE, and ventilatory demand were statistically higher in ADL2 and ADL3 compared to ADL1 (Figure 3). Metabolic demand and other variables presented similar behavior in all ADL (Table 2).

Table 2. Comparison between three ADL in relation to oxygen saturation, heart rate, dyspnea, ventilatory and metabolic variables.

n=48	ADL 1	ADL 2	ADL 3
SpO ₂ , %	90.79±4.47	90.5±4.87	91.65±4.88†
Δ SpO ₂ , %	-3.18±3.45	-3.47±3.99	-2.33±4.05†
Oxygen desaturation, n(%)	20 (41.7)	16 (33.3)*	12 (25)*†
HR, bpm	95.48±14.52	99.83±14.97*	98.61±14.38*
HR _{ADL} /HR _{max} , %	63.81±9.78	66.83±10.26*	65.89±9.64*
Dyspnea, BORG	1.52±1.29	1.80±1.59	1.80±1.46
Fatigue, BORG	0.78±1.02	0.94±1.19	1.07±1.39
VE, L/min	22.06±6.77	23.77±6.52*	24.03±6.88*
VE _{ADL} /MVV, %	47.9±22.89	52.15±26.38*	52.66±27.03*
VO ₂ , L/min	0.84±0.40	0.87±0.35	0.84±0.37
VO ₂ , ml/kg.min	12.61±6.04	13.20±5.53	12.77±5.94
VO _{2ADL} /VO _{2peak} , %	90±51.24	91.03±30.99	88.90±42.41
MET	3.60±1.72	3.77±1.58	3.65±1.69

Values expressed as mean ± standard deviation. **Legend:** ADL=activities of daily living; ADL1=taking shower; ADL2= containers above scapular girdle; ADL3= pots below pelvic girdle; HR= heart rate; VE= pulmonary ventilation; MVV= maximal voluntary ventilation; VO₂= oxygen consumption; MET= metabolic equivalent. Percentage differences: Chi-square test; Media differences: ANOVA repeated measures test=*p<0.05; significant differences between ADL1 vs ADL2 and ADL3; †p<0.05: significant differences between ADL2 vs ADL3.

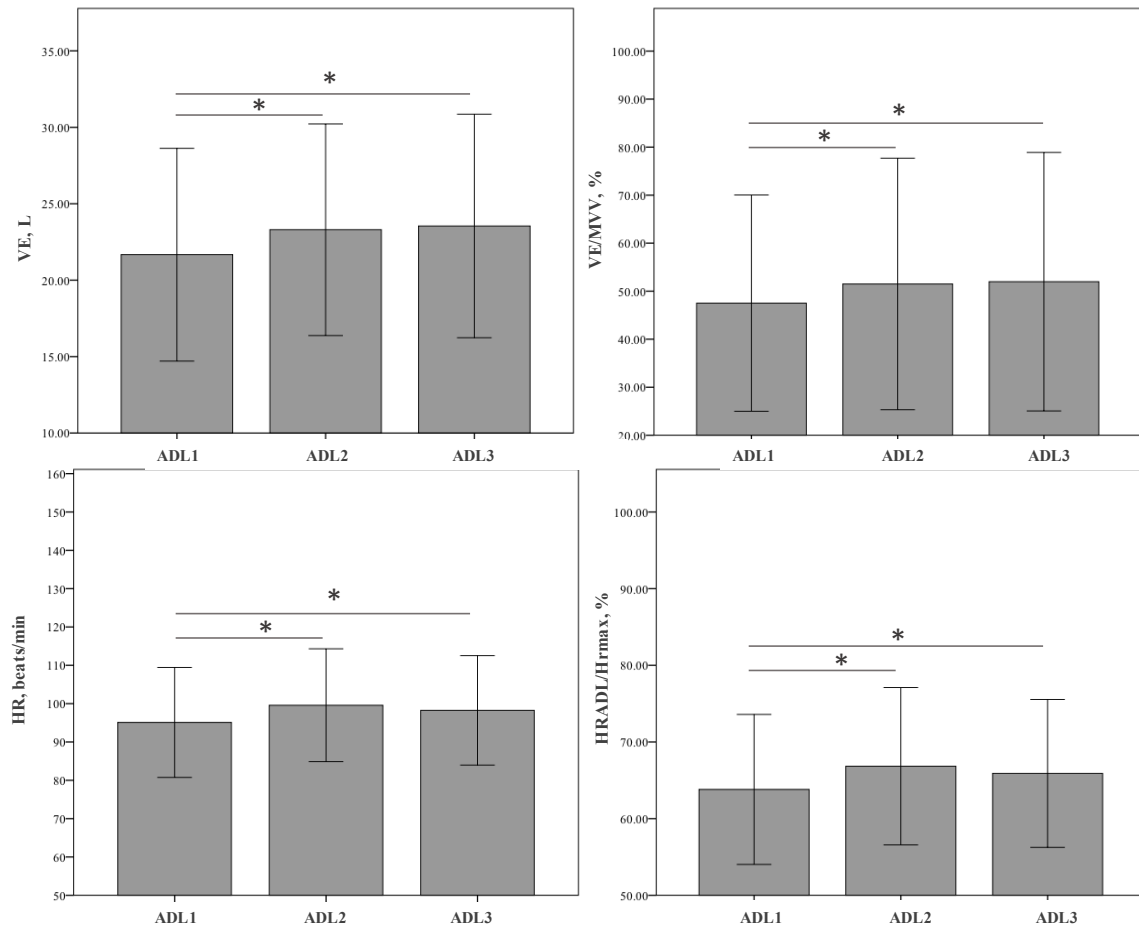


Figure 3. Ventilatory and cardiac variables in each ADL. **Legend:** VE: ventilation; MVV: maximum voluntary ventilation; HR: heart rate; **ADL1:** taking shower; **ADL2:** containers above scapular girdle; **ADL3:** pots below pelvic girdle. * $p < 0.05$: ANOVA repeated measures test.

Correlation between LCADL and SGRQ with the ADL limitations

The percentage score obtained in the LCADL (LCADL%) showed a moderate correlation with dyspnea in ADL3 ($p=0.008$; $r=0.40$) and metabolic demand in ADL1 ($p=0.006$; $r=0.475$), besides weak correlation with dyspnea in ADL1 ($p=0.032$; $r=0.311$) and ADL2 ($p=0.020$; $r=0.334$), as we can see in Figure 4.

The SGRQ score demonstrated a moderate correlation with dyspnea in ADL1 ($p=0.001$; $r=0.465$), ADL2 ($p < 0.001$; $r=0.514$), and ADL3 ($p < 0.001$; $r=0.642$), and with metabolic demand in ADL1 ($p=0.012$; $r=0.439$) and ADL3 ($p=0.019$; $r=0.413$). In addition, the SGRQ showed a weak correlation with fatigue in ADL2 ($p=0.036$; $r=0.304$) and ADL3 ($p=0.017$; $r=0.344$) and with ventilatory demand in ADL2 ($p=0.046$; $r=0.290$) and ADL3 ($p=0.014$; $r=0.351$) (Figure 4).

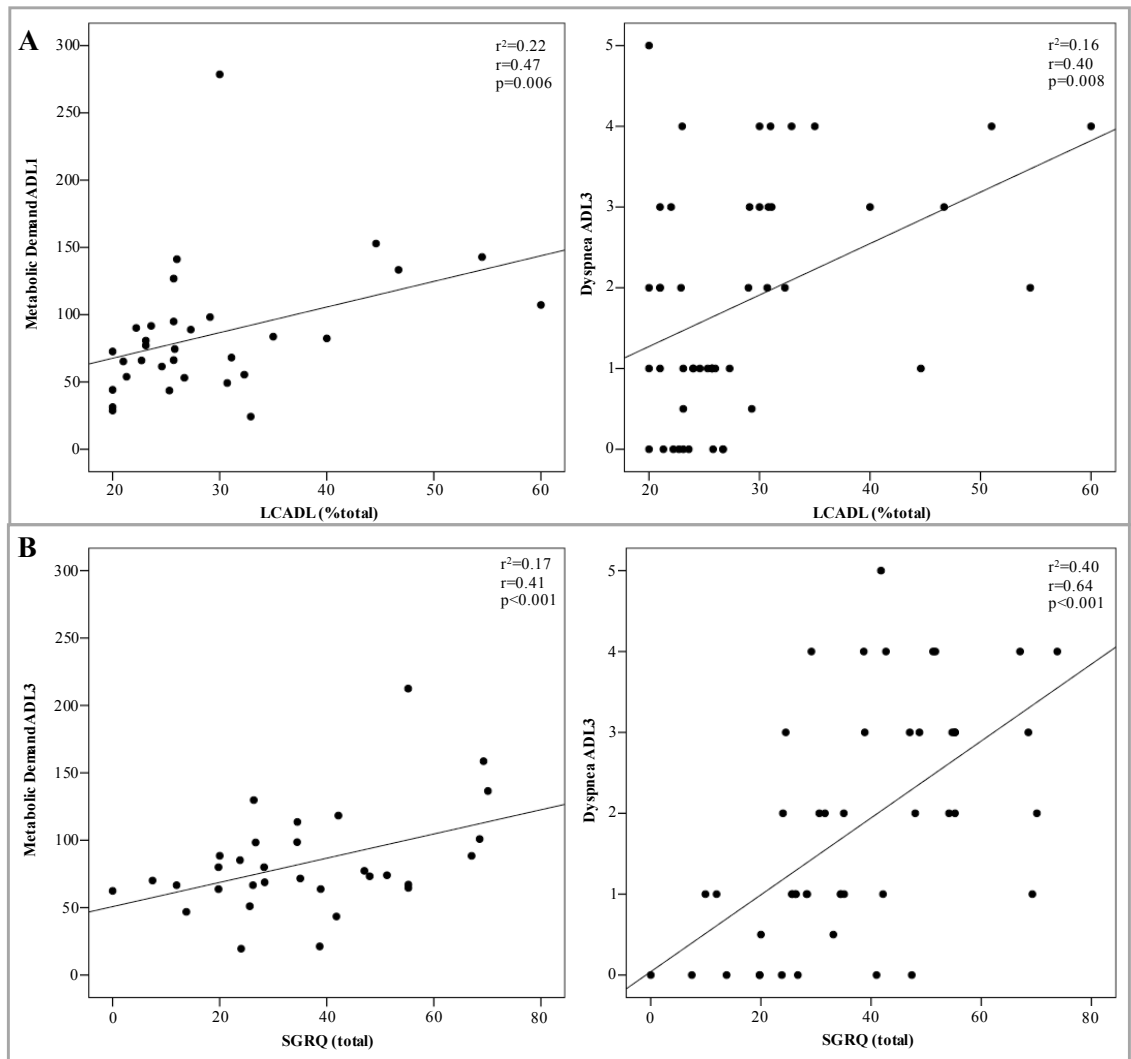


Figure 4A. Correlation between LCADL (%total) and metabolic demand in ADL1 and Dyspnea in ADL3. **4B.** Correlation between SGRQ (total) and metabolic demand and dyspnea in ADL3. **Legend:** LCADL: London Chest Activity of Daily Living; SGRQ: Saint George Respiratory Questionnaire; ADL1: taking shower; ADL3: pots below pelvic girdle.

The variability of dyspnea in ADL3 and metabolic demand in ADL1 ($p=0.026$) explained 33% of the variability in LCADL%. The variability of dyspnea and metabolic demand in ADL 3 ($p<0.001$) explained 67% of the variability in SGRQ (Table 3).

Table 3. Stepwise linear regression model for SGRQ and LCADL

Stepwise regression	SGRQ					r ²	p-value
	Coefficient	SE	t-value	CI 95%			
Dyspnea ADL3, index	9.15	1.40	6.52	6.25 to 12.21	0.672	<0.001	
Metabolic demand ADL3, %	0.23	0.05	4.58	0.11 to 0.34			
	LCADL						
Dyspnea ADL3, index	3.05	1.06	2.86	0.86 to 5.23	0.339	0.008	
Metabolic demand ADL1, %	0.07	0.03	2.34	0.01 to 0.13		0.026	

Multiple linear regression model for parameters predictive of SGRQ and LCADL. **Legend:**ADL=activities of daily living; ADL1=taking shower; ADL3= pots below pelvic girdle.

Discussion

The main results of this study were that the ADL involving trunk flexion and rotation and unsupported upper limb movements led to lower values of SpO₂, and higher ventilation and metabolic demand values. It is also noted that ADL1 presented the highest percentage of patients with oxygen desaturation, and metabolic demand values were close to 90% during the ADL. In addition, dyspnea and metabolic demand in ADL3 were able to explain 67% of the SGRQ score and dyspnea in ADL1 and metabolic demand in ADL3 explained 34% of the LCADL score.

The activities of showering, lifting container above the shoulder girdle, and lowering pots below the pelvic girdle were chosen because some studies have shown that they are capable of leading to greater increases in ventilation and oxygen consumption^{10,11}.

Annegarn et al.¹⁷ observed that among 820 patients classified as GOLD IV, self-care ADL, such as showering, personal hygiene, and basic home maintenance were those classified as the most problematic. In addition, showering was classified as the fourth most problematic activity in this population. The study concluded that the clinical characteristics are weakly associated with problematic ADL, emphasizing the individual assessment of these activities in order to plan a personalized intervention.

Regarding disease severity, Castro et al.¹⁰ showed that the worse severity the higher metabolic and ventilatory demand to perform ADL; consequently, the lower ventilatory and aerobic reserve. Mild COPD patients achieved 20% of the metabolic demand while severe patients achieved values close to 80%. In our study 48% were moderate and 52% were severe and very severe COPD patients. Contrasting with the literature, the patients of the present study achieved values near to 90% of metabolic demand, demonstrating that the execution of ordinary

activities leads to oxygen consumption close to VO_{2peak} . This suggests that when patients are performing certain ADL they do so close to their tolerable limit.

Higher metabolic demand during ADL has already been described^{18,19}. When patients performed more vigorous activities²⁰ than those selected for the present study, they reached 75.4% to 85% of metabolic demand. Despite the fact that the activities selected for this study are not considered as intense as in the other study, patients reached higher values of metabolic demand. This allows us to infer that despite the ADL classification of moderate or vigorous activities, it is necessary to consider the nature of ADL in specific population. In our study, the ADL included a great range of upper limb motions combined with trunk flexion and rotation, so high metabolic demand was necessary to perform the ADL.

Associated with the high metabolic demand, a high value of MET, to perform the ADL was verified by the present study. These values were twice higher than those expected to health subjects²⁰, thus, ADL that were previously classified as mild activities are classified as moderate for our patients. Systemic inflammation, oxidative stress and muscle peripheral impairments have an adverse effect on respiratory and peripheral muscle function and thus affects exercise capacity²¹, leading to high values of oxygen consumption and a higher MET to do mild activities.

Concerning ventilatory demand, Castro et al.¹⁰ found values close to 54% for severe patients. Some studies^{11,13} reported that severe and very severe COPD patients reached values close to 50% of ventilatory demand when sweeping the floor and placing containers on high shelves. Moreover, they showed a relationship between metabolic and ventilatory demand with disease severity. These findings corroborate the results of the present study, in which moderate to very severe COPD patients reached 52% of ventilatory demand in activities encompassing upper and lower limb movements associated with trunk inclination and rotation. This reinforces the idea that this type of activity can lead to ventilatory reserve reduction, causing limitations in its execution. It is known that dynamic hyperinflation occurs during ADL and may contribute to performance limitation²²⁻²⁴, however, we did not measure this component during our simulation.

Despite high metabolic and ventilatory demand, the onset of dyspnea, and oxygen desaturation, the HR was not so high. Patients achieved values close to 65% of HR_{max} , with lower values in ADL1, and these values are similar to those found in the literature^{10,11}

during ADL simulation. As a limitation, we just assessed the HR during ADL, which do not allow us to infer concerning cardiac demand impairment.

In the present study, we found a correlation between metabolic limitations (increased metabolic demand) and ventilatory limitations (dyspnea and increased ventilatory demand during ADL) with the quality of life through the SGRQ score. From this finding, it can be stated that when we apply SGRQ, the total score is associated with the real limitation during the performance of ADL, being that SGRQ score reflected 67% of the real limitations during ADL such as increased metabolic demand and dyspnea. Although it is known that dyspnea is related to the real limitations in the ADL performance²⁵, this is the first study to show the relationship between SGRQ score and real limitations during ADL.

Regarding the assessment of ADL limitations, it is known that specific assessments of ADL are not always possible and questionnaires and scales are commonly used. It has been described that dyspnea reported during the performance of ADL may not be related to dyspnea assessed by scales, such as the mMRC⁵. This finding contrast with the present study, wherein ADL limitation verified by LCADL showed correlation with dyspnea, and metabolic and ventilatory demands during ADL. This can be explained as the LCADL scale involves four domains of 15 ADL, being much more comprehensive than the mMRC. Moreover, the ADL included in the LCADL are similar to the ADL selected by the present study, reflecting ADL commonly performed by the patients in “real life”. The present study found that LCADL score was able to explain 33% of the increase in metabolic demand and dyspnea in all three ADL.

Although ADL assessment through simulation requires a longer time and adequate environment, often making it unfeasible, present study allows us to infer that if there is no possibility to perform ADL simulation the use of specific scales and questionnaires, such as LCADL and SGRQ can be performed, since these tools represent and reflect the real limitations of the patients during ADL.

Dyspnea is related to the real limitations that patients experience during the performance of ADL, generally becoming a limiting factor²⁵. Accurate assessment of dyspnea during ADL will allow more adequate therapeutic management, avoiding the increase in dyspnea leading to a reduction in the quantity of ADL, decreasing functionality and having a clear impact on quality of life.

We should consider as a limitation of the study the attainment of VO_{2peak} from a symptom-limited cardiopulmonary test performed on a cycle ergometer, which leads to lower

values of VO_{2peak} , in addition to recruiting a smaller muscle group. However it is commonly used in COPD patients, being described as a tool to evaluate and even compare with ADL¹⁹. Another possible limitation was the fact that some ADL lasted less than five minutes, a time necessary to reach the steady state of metabolic and ventilatory demands. However, the idea of ADL simulation was conceived to represent, in the most faithful way, its real-life execution.

Clinical implication

In the clinical practice we strongly recommend that the use of SGRQ and LCADL, as we can see in the present study, reflect some functional limitation during a “real life” situation. We should consider that tools are non-expensive, valid, reliable and responsive.

Considering our study, we cannot give a cutoff point to SGRQ and LCADL because it was not our aim. As a clinical implication of the present study, if some limitation are found in the LCADL and SGRQ, is important to give an attention to this, as we know patients usually present limitation at the very early stage of efforts²⁶.

Based on this, we recommend that some energy conservation techniques (ECT) should be taught to these patients. As we know, ECT are recommended in pulmonary rehabilitation programs, and these techniques are able to decrease tiredness and make these patients more independent to perform ADL, as described by Velloso & Jardim²⁶.

The therapist should instruct the patient to adapt their home to do all ADL in the easiest way, as an example, during the shower the patient could use a chair to seat, and instead of bench his/her body to wash the lower limbs, the patient can be instructed to flex the hip and knee, crossing one leg over the other, without bending forward during the whole activity. The same position can be adopted to put shoes on and off²⁶.

During the personal hygiene activities, the adaptation could be sit in front of the sink and rest their arms on its edge, and also put the mirror in a lower position²⁶. When the activities involve unsupported upper limbs movements, the patient could adapt the shelves to a lower position, avoiding movements above the shoulders. The same adaptation could be done to activities that involve bending and trunk rotation, changing the positions of shelves and instead to bending forward squatting.

Furthermore, the inclusion of exercises with more functional characteristics, in which the goal is to improve the performance in ADL, should be considered in pulmonary rehabilitation programs. The use of upper limbs exercises to increase muscle endurance and

strength is so relevant, which would improve the performance in ADL with unsupported upper limbs²⁷.

Conclusion

In conclusion, ADL involving flexion and trunk rotation associated with unsupported upper limb elevation were able to identify the patients who presented oxygen desaturation and high ventilatory demand. In total, 20-40% of the patients presented oxygen desaturation during these ADL. High metabolic demand was verified during all ADL performance. LCADL and SGRQ are tools able to reflect functional limitation during ADL such as dyspnea and the metabolic demand during ADL. These functional limitations are reflected 67% in the SGRQ score, showing SGRQ to be better than LCADL for reflecting ADL limitations. Thus, LCADL and SGRQ represent important tools used in clinical practice they were able to reflect ADL limitations.

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Chapter 3

Different intensities of resistance training and the impact on health status focusing on activities of daily living in patients with COPD: a randomized controlled parallel study

In this chapter, we will describe the aim, methods, results and discussion from the manuscript titled Different intensities of resistance training and the impact on health status focusing on activities of daily living in patients with COPD: a randomized controlled parallel study

This manuscript has been submitted to Clinical Rehabilitation (manuscript number: CRE-2018-6923).

There is no clear and consensual understanding regarding the comparison between different intensities of resistance training and improvements in ADL performance, dyspnea, and health status in COPD patients. Thus, the aim of our study were to investigate whether two different resistance training intensities improve health status, more specifically ADL performance, dyspnea, and quality of life, followed by improvement in exercise capacity and muscle strength as well as to verify if there is a superior effect of either of these resistance training intensities on these outcomes. We hypothesized that low/load and high repetition training would present a higher effect in health status.

Methods

Experimental Design

A randomized, parallel-group, single center trial was conducted with COPD patients at the Laboratory of Spirometry and Respiratory Physiotherapy of the Federal University of São Carlos - UFSCar, SP, Brazil, from October 2013 to April 2016. Patients were recruited from the UFSCar rehabilitation center and through medical referral. The Ethics Committee from the university approved the study (0354.0.135.000-11) and it was registered in Clinical Trials (NCT01977469).

The assessments were performed on three non-consecutive days with a 48-h interval between assessments. On the first day, the simulation of a set of ADL and the 6-minute walk test (6MWT) were performed and all the patient-reported measures were collected. On the second day, an isometric shoulder flexor test and a symptom-limited cardiopulmonary exercise test (CPET) were performed. Finally, on the third day a one-repetition maximum test (1RM) was performed. After the assessment, patients were randomly allocated into two different exercise training protocols.

Participants

A convenience sample of 45 patients was included according to the following inclusion criteria: men or women with a confirmed diagnosis of moderate to severe COPD¹; aged 60 years or over; former smokers; and no change in medication or clinical stability for at least 2 months. The exclusion criteria were: severe heart disease or any other pathology that did not allow the performance of the proposed tests; presence of cardiovascular, neurological, musculoskeletal, metabolic, or rheumatologic comorbidities that could influence any of the outcomes; participation in any pulmonary rehabilitation program completed in the previous six months; and an episode of exacerbation of clinical symptoms during the study.

Exercise training protocol

Both training exercise protocols consisted of 1-hour training sessions, three times/week, for 12 weeks, with a sum of 36 supervised sessions. Patients were randomly allocated into two groups, which differed due to the load in the resistance training: low-load/high-repetition (LL/HR) and high-load/low-repetition (HL/LR). The randomization scheme was generated using a website (www.randomization.com). The sequence was concealed until the intervention was assigned and the physiotherapist was not blinded to group allocation.

All patients performed the same 20-minute aerobic training protocol on a cycle ergometer. The initial load was 80% of VO_{2peak} , and the intensity progression was performed according to patient tolerance (BORG scale between 4 and 6).

The resistance training was performed for chest press, high pulley, and leg press. The LL/HR was designed to facilitate an effect on peripheral muscle endurance², with an initial load (30%1RM) in combination with a high number of repetitions (15 repetitions) and standardized volume of 15 repetitions * 3 sets. The HL/LR aimed at gains in muscle strength², with an initial load of 60%1RM in combination with a low number of repetitions (8 repetitions) and standardized volume of 8 repetitions * 3 sets. Both training programs allowed a two minute rest interval between sets and the intensity progression was progressively increased each nine sessions up to: - LL/HR: upper limbs: 45% and lower limbs: 51%; - HL/LR: upper limbs: 75% and lower limbs: 81%³ (table 1S).

Table 1S. Workloads increased and training characteristics

TRAINING PROTOCOL	
Frequency	3 times per week (alternate days, consecutive weeks)
Duration	50 to 60 min per session for 36 sessions
Aerobic Training	
Modality	Cycle ergometer
Duration	20 to 30 minutes
Type	Continuous
Initial intensity	Load in 80% of the peak VO ₂ in CPET
Intensity progression	According to patient tolerance, flowing the criteria: - Symptom: BROG scale 4-6 - HR < 85% HR _{max} predicted - SpO ₂ > 90% - BP < 180x100 mmHg
Resistance Training	
Modality	Upper limbs: Chest Press and High Pulley Lower limbs: Leg Press
Sets/repetition	LL/HR: 3 sets/15 repetition HL/LL: 3 sets/8 repetition
Interval between sets	2 minutes
Initial load	LL/HR: 30% 1RM HL/LL: 60% 1RM
Intensity progression	Upper limbs: + 5% every 9 sessions LL/HR: 30%→35%→40%→45% 1RM HL/LL: 60%→65%→70%→75% 1RM Lower limbs: + 7% each 9 sessions LL/HR: 30%→37%→44%→51% 1RM HL/LL: 60%→67%→74%→81% 1RM
Comments	Monitoring of signs (HR, SpO ₂ and BP) and symptoms (dyspnea and fatigue) Instruction to movement performance each exercise during expiratory phase, avoiding Valsalva Maneuver
Abbreviations HR= heart rate; SpO ₂ = oxygen saturation; BP= blood pressure; LL/HR= low-load/high-repetition; HL/LR= high-load/low-repetition; 1RM= 1-repetition maximum	

Assessments

At inclusion in the study, patients performed a CPET and 1RM test to determine the training load. The CPET was performed on a cycle ergometer with a metabolic system (VO₂₀₀₀ Exercise Testing System - MedGraphics), and gas samples were collected from an average of three breaths. Patients began the test sitting on the cycle ergometer, with a three minute rest followed by a one minute warm-up with subsequent load increases of five watts every two minutes. Patients were instructed to maintain a pedaling cadence from 50 to 60 rpm. The criterion for interrupting the test was according to the American Thoracic Society/American College of Chest Physicians⁴.

The 1RM test was performed for chest press, high pulley, and leg press. A warm-up was carried out, with ten load-free repetitions performed in the equipment. Subsequently, a crescent protocol started with an initial load defined as 40% of the body weight for upper limbs and 60% of the body weight for lower limbs. The test was executed until there was failure in one attempt and the 1RM was considered as the final successful attempt. A maximum of six attempts were accepted for determination of the 1RM^{5,6}, otherwise the patient was required to finish the test on another day.

Outcomes

ADL performance - ventilatory demand and ventilatory efficiency - and LCADL scale was considered one of the primary outcomes of the study. The six-minute walk distance (6MWD), isometric shoulder flexor strength and SGRQ were considered as secondary outcomes of the study.

Health status assessment

The three sub-classifications of health status in COPD proposed by Vercoulen and colleagues⁷ were assessed: physiological functioning (exercise tolerance, ADL ventilatory and metabolic parameters, muscle function), complaints ((expected) dyspnea and dyspnea during ADL), and quality of life (health-related quality of life).

- Physiological functioning

The ADL assessment was carried out in a house simulation laboratory. Patients were instructed to get out of bed, put on their shoes, make the bed, shower, lift and lower containers from a shelf above the shoulder girdle, and raise and lower pots from a shelf below the pelvic girdle⁸. All these ADLs have been identified as problematic^{9,10}.

The ADL simulations were all accompanied by the same evaluator, and patients were instructed to perform them in the aforementioned order, as a circuit, as performed at home, with no time limit for their execution. The runtime was recorded to compare the total time before and after the rehabilitation.

The simulation was carried out with a metabolic system (VO₂₀₀₀ Exercise Testing System - MedGraphics). Metabolic and ventilatory variables; ventilation (VE), oxygen consumption (VO₂), ventilatory efficiency (VE/VCO₂), and metabolic equivalent (MET) were collected. For the statistical analyses, the mean value for each variable was calculated, using all the points given by the metabolic system during the circuit. Maximal voluntary ventilation

(MVV) was obtained by the equation $FEV_1 * 37.5^{11}$ and ventilatory demand (VE_{ADL}/MVV) was subsequently calculated.

Furthermore, oxygen saturation (SpO_2) was measured with a pulse oximeter at rest and immediately after the end of the circuit. ΔSpO_2 was calculated at the end of the circuit using the equation: $\Delta SpO_2 = SpO_{2\text{final}} - SpO_{2\text{rest}}$.

The exercise tolerance was assessed by the 6MWT, performed according to the standards of the European Respiratory Society and American Thoracic Society¹². Two tests were performed with a 30-minute interval between attempts and the longest distance was considered for the statistical analyses, in addition, a percentage of predicted was determined¹³ and an increase in 25 meters after training was considered as minimal important difference (MID)¹⁴.

The isometric shoulder flexor test was used to assess muscle function, with a hand-held dynamometer (Microfet 2, Hoggan – Health Industries, West Jordan, UT, USA). This muscle group was chosen as it has great involvement in the execution of ADLs, especially in unsupported arm activities^{8,15}. Participants were tested in the supine position, with the shoulder flexed at 90° and elbow extended, the dynamometer positioned just proximal to the epicondyles of the humerus and stabilization was carried out in the axillary region, as described by Andrews and colleagues¹⁶. Patients were instructed to perform a maximum contraction during 4 seconds, securing maximum muscle-fibers recruitment. Three repetitions were conducted until reproducible measurements were obtained, and the highest value was used for analysis. To avoid muscle fatigue, a 60-sec rest-interval between contractions was allowed¹⁷.

- Complaints

All the patient-reported measures were applied in the form of an interview in a quiet environment, always by the same examiner and translated and validated for the Brazilian population¹⁸⁻²¹.

To assess dyspnea, the mMRC was used. This instrument presents a score from 0-4 and a 1-point reduction after an intervention was considered as the MID^{18,22,23}.

The LCADL assesses limitations to perform ADLs and a higher total score indicates greater limitation in performing ADLs due to dyspnea²⁴. It is composed of four domains: self-care, domestic activities, physical activities, and leisure. A total score and

percentage of total can be calculated²⁴ and a 4-point reduction is considered the minimal detectable change (MDC)²⁵.

Dyspnea during the ADL simulation was also assessed by the modified Borg 0-10 scale, measured before and after the simulation. The values at the end of the circuit were used to compare dyspnea pre- and post- exercise training.

- Quality of life

Health-related quality of life was assessed by the SGRQ, which addresses aspects related to three domains; respiratory symptoms, changes in physical activity, and the overall impact on ADL and patient well-being, assessing quality of life. Higher scores are related to poorer quality of life^{19,26} and a 4% reduction was considered as MID²⁷.

Sample size calculation

The sample size was calculated using pilot data from the first four subjects allocated to the LL/HR and four allocated to the HL/LR group using G*Power 3.1 software²⁸. For this calculation, the LCADL total was considered as this variable presented the highest sample size after calculation. The mean and standard deviation from these pilot data are presented in Table 2S. For this calculation, the F-test (repeated measures ANOVA, within and between factors) was used and a power of 0.80 and alpha of 0.05, with a loss of 15% of the data were considered, requiring a total sample size of 34.

Table 2S. Pilot data for sample size calculation.

Group	LL/HR		HL/LR	
	Pre	Post	Pre	Post
LCADL total	18.5 ±7	15 ±6.05	15.5 ±1	12.25 ±1.25

Data expressed as mean ± SD. LL/HR: low-load/high-repetition; HL/LR: high-load/low-repetition.

Statistical Analysis

A mixed model, two-way analysis of variance (group and evaluation time) with repeated measurements (evaluation time: pre- and post- LL/HR and HL/LR) was used to examine the effects of group-by-evaluation time interaction, group (LL/HR and HL/LR), and evaluation time (before and after rehabilitation). Furthermore, the partial eta squared (η^2) was used to determine the effect size of the interaction²⁹. By convention, an η^2 around 0.2, 0.5, and 0.8 were considered small, medium, and large, respectively³⁰. Data are presented as mean (SD), unless noted otherwise.

The difference between pre- and post-training measures was determined through subtraction of the post-training mean value by the pre-training mean value for each variable expected to increase after the intervention, or the subtraction if a reduction in the final value after the intervention was expected. Subsequently, the obtained differences were compared with the MID/MCD established by the literature and patients were divided into those who achieved MID/MCD values and those who did not. These binomial proportions were compared between two groups of exercise (LL/HR and HI/LR) using the Chi-Square test of homogeneity.

All statistical tests were carried out using SPSS software version 25 (SPSS Inc, Chicago, IL, USA), and the significance level was set at 0.05.

Results

Participants

A total of 34 patients were included in the study. Of these, 17 were allocated to LL/HR and 17 to HL/LR. In the LL/HR, 13 patients completed the intervention and were reassessed for the primary outcome (ADL simulation) and 11 in the HL/LR. Figure 1 presents the reasons for the drop-outs.

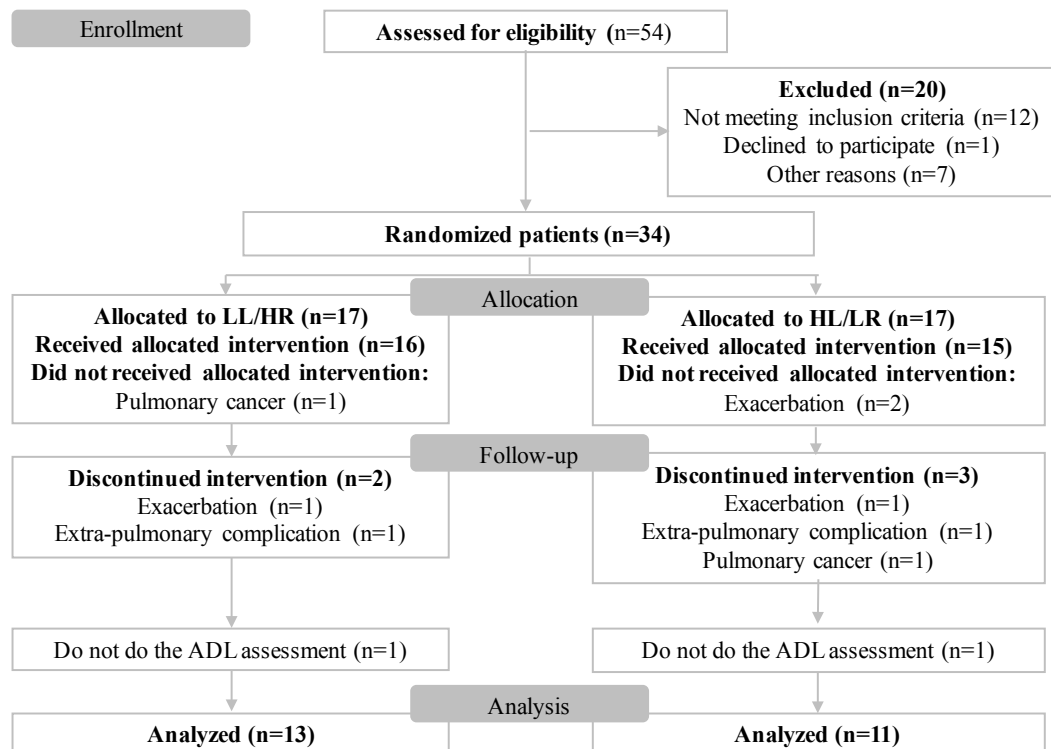


Figure 1. Flow-chart of patient's inclusion. **Abbreviations:** LL/HR= low-load/high-repetition resistance training; HL/LL= high-load/low-repetition resistance training; ADL= activities of daily living.

Baseline characteristics

On average, patients were more than 65 years of age, with moderate-to-severe COPD, impaired exercise capacity, and experienced mild problems during the performance of ADLs, assessed by the mMRC (table 1). There were no differences concerning the baseline characteristics between groups.

According to the combined assessment proposed by GOLD in 2011³¹ in the LL/HR, 1 patient was GOLD-A, 4 patients GOLD-B, 3 patients GOLD-C, and 4 patients GOLD-D and in the HL/LR, 1 patient was GOLD-A, 2 patients GOLD-C, and 8 GOLD-D.

Table 1. Baseline characteristics of COPD patients randomly assigned to low-load/high-repetition (LL/HR) and high-load/low-repetition (HL/LR)

	LL/HR n= 13	HL/LR n= 11
Sex		
Male, n (%)	10 (76.9)	9 (81.9)
Female, n (%)	3 (23.1)	2 (18.2)
Age, y	68.62±8.7	69.09±6.87
FEV ₁ , l	1.37±0.54	1.35±0.60
FEV ₁ , % predicted	49.95±16.22	50.24±15.01
FEV ₁ /FVC, %	53.16±11.66	53.27±10.57
GOLD classification, n (%)		
2: moderate	4 (30.8)	2 (18.2)
3: severe	8 (61.5)	9 (81.8)
4: very severe	1 (7.7)	0
Charlson index	1.46±0.66	1.73±0.78
Diabetes, n (%)	1 (7.69)	1 (9.09)
Controlled Systemic Hypertension, n (%)	3 (23.07%)	3 (27.27)
Vascular disease, n (%)	1 (7.69)	1 (9.09)
Ischemic heart disease, n (%)	1 (7.69)	0
Gout, n (%)	0	1 (9.09)
Stroke without sequel, n (%)	1 (7.69)	0
Smoke history, packs.year	77.26±32.18	67.04±28.03
MRC dyspnea grade	1 (1-3)	2 (1-3)
Exacerbation <12m, n (%)	7 (53.8%)	8±72.7
BMI, kg.m ⁻²	24.54±3.67	26.63±5.50
6MWD, m	396.15±112.73	399.0±81.43
6MWD, % predicted	69.63±18.39	72.22±15.37
BODE index	3 (2-4)	2 (1-4)
Maximum load CPET, watts	33.08±17.38	31.36±10.97
VO _{2peak} CPET, ml.kg ⁻¹ .min ⁻¹	12.64±4.42	13.62±4.38
Medication, n (%)		
Bronchodilator + inhaled corticosteroids	13 (100)	11 (100)

Data expressed as mean±SD, median (Q1-Q3) or number of patient (%). **Abbreviations:** MMRC= medical research council dyspnea grade; BMI= body mass index; 6MWD= six-minute walk distance; CPET= cardiopulmonary exercise test. * Non-significant differences between groups for all variables.

Effects of the exercise training protocol in health status

The overview of the results of the mixed two-way ANOVA can be found in

Table 2S.

Table 3S. Overview of the results of mixed two-way ANOVA for ADL, patient-reported and performance-driven measures

Parameter	Measure	Effect of Time				Effect of Time X Training				Effect of Training			
		df	F	P value	Partial η^2	df	F	P value	Partial η^2	df	F	P value	Partial η^2
<i>Physiological functioning</i>													
<i>Exercise tolerance</i>	6MWD, meters	1	5.782	0.025*	0.208	1	0.804	0.380	0.035	1	0.029	0.866	0.001
	6MWD, % predicted	1	5.948	0.023*	0.213	1	0.729	0.402	0.032	1	0.026	0.873	0.001
<i>Muscle strength</i>	Shoulder flexor, N	1	38.179	0.000*	0.634	1	0.444	0.512	0.020	1	0.285	0.599	0.013
	Shoulder flexor, %	1	30.738	0.000*	0.583	1	1.256	0.274	0.054	1	1.842	0.188	0.077
<i>ADL simulation</i>	SpO ₂ , %	1	6.065	0.022	0.216	1	0.615	0.441	0.274	1	0.373	0.547	0.017
	Δ SpO ₂ , %	1	1.156	0.697	0.007	1	0.639	0.433	0.028	1	2.38	0.136	0.098
	VE, l	1	0.007	0.935	0.000	1	0.063	0.804	0.003	1	0.371	0.549	0.017
	VE/MVV, %	1	0.159	0.694	0.007	1	0.001	0.972	0.000	1	0.272	0.607	0.012
	VO ₂ , l/min	1	0.301	0.589	0.014	1	1.491	0.235	0.063	1	1.766	0.198	0.074
	VO ₂ , ml.kg/min	1	0.247	0.624	0.011	1	0.564	0.461	0.025	1	0.776	0.388	0.034
	VE/VO ₂	1	0.372	0.548	0.017	1	3.771	0.065	0.146	1	2.630	0.119	0.107
	VE/VCO ₂	1	0.598	0.447	0.026	1	3.116	0.091	0.124	1	0.695	0.413	0.031
	MET	1	0.285	0.599	0.013	1	0.649	0.429	0.029	1	0.812	0.377	0.036
	Total time, sec	1	0.671	0.422	0.030	1	0.586	0.451	0.026	1	0.147	0.705	0.007

(Continued)

Table 3S. (Continued).

Parameter	Measure	Effect of Time				Effect of Time X Training				Effect of Training			
		df	F	P value	Partial η^2	df	F	P value	Partial η^2	df	F	P value	Partial η^2
Complaints													
	mMRC	1	3.412	0.078	0.134	1	0.024	0.879	0.001	1	0.646	0.430	0.029
	LCADL												
	- <i>Self-care</i>	1	2.358	0.139	0.097	1	1.681	0.208	0.071	1	0.007	0.934	0.000
	- <i>Domestic</i>	1	2.720	0.113	0.110	1	0.447	0.511	0.020	1	0.136	0.716	0.006
	- <i>Physical</i>	1	9.644	0.005*	0.305	1	0.086	0.772	0.004	1	0.151	0.702	0.007
	- <i>Leisure</i>	1	2.097	0.162	0.087	1	0.163	0.690	0.007	1	0.016	0.901	0.001
	- <i>Total</i>	1	7.260	0.013*	0.248	1	0.019	0.893	0.001	1	0.030	0.864	0.001
	- <i>%Total</i>	1	4.802	0.039*	0.179	1	0.151	0.701	0.007	1	0.083	0.776	0.004
<i>ADL simulation</i>	Dyspnea	1	9.829	0.005*	0.309	1	0.398	0.534	0.018	1	0.058	0.812	0.003
Quality of Life													
	SGRQ												
	Symptoms	1	9.001	0.007*	0.290	1	4.232	0.050*	0.161	1	0.341	0.565	0.015
	Activities	1	0.411	0.528	0.018	1	0.765	0.391	0.034	1	0.324	0.575	0.015
	Impact	1	1.745	0.200	0.073	1	2.031	0.168	0.085	1	0.427	0.520	0.019
	Total	1	3.187	0.088	0.127	1	0.921	0.348	0.040	1	0.193	0.664	0.009

Legend: 6MWD: six-minute walk distance; SpO₂= oxygen saturation; VE= pulmonary ventilation, MMV= maximal voluntary ventilation; VO₂= oxygen consumption; MET= metabolic equivalent; mMRC= medical research council dyspnea grade; LCADL= London Chest Activity of Daily Living Scale; SGRQ= Saint George's Respiratory Questionnaire. Two-way repeated measures analysis of variance: *p<0.05.

- Physiological functioning

There were no statistically significant interactions between the intervention and time on oxygen saturation, or ventilatory and metabolic variables during ADL. The main effect of training showed that there were no statistically significant differences in oxygen saturation, or ventilatory and metabolic variables during ADL (Table 3S).

There were no statistically significant interactions between the intervention and time in the 6MWD and shoulder flexor strength (Tables 2 and 3S).

The main effect of time was statistically significant for the 6MWD ($F=5.782$, $p=0.025$, partial $\eta^2=0.208$ and observed power=0.63) and for shoulder flexor strength ($F=30.738$, $p<0.001$, partial $\eta^2=0.583$, observed power=1), with no statistically significant main effect of intervention (Tables 2 and 3S).

Table 2. Physiological functioning of COPD patients randomly assigned to low-load/high-repetition (LL/HR) and high-load/low-repetition (HL/LR) pre- and post-exercise training

	LL/HR (n=13)		HL/LR (n= 11)	
	Pre-	Post-	Pre-	Post-
Exercise tolerance				
6MWD, meters	396.15±11.73	429.69±85.65*	399.0±81.43	414.31±86.82*
Muscle strength				
Shoulder flexor, N	105.38±37.85	125.53±35.84*	114.19±22.19	130.42±28.05*
Shoulder flexor, %	51.16±15.65	61.33±14.48*	60.54±15.23	67.28±10.89*
ADL simulation				
SpO ₂ , %	90.4±5.08	90.15±4.67	91.65±2.92	92.07±2.49
Δ SpO ₂ , %	-3.52±3.94	-2.76±2.15	-2.76±2.27	-1.38±2.30
VE, l/min	19.81±6.82	19.39±6.48	20.82±3.86	21.03±6.74
VE/MMV, %	44.91±26.94	43.66±24.54	50.90±30.40	49.40±33.28
VO ₂ , l	0.69±0.22	0.66±0.21	0.75±0.18	0.84±0.32
VO ₂ , ml.kg/min	10.39±4.23	10.19±4.36	11.26±4.27	12.23±4.89
VE/VCO ₂	30.75±3.60	33.51±5.27	37.93±18.30	30.85±3.48
MET	2.96±1.21	2.90±1.24	3.21±1.22	3.5±1.39
Total time, sec	899.53±188.20	848.30±240	849±139.81	848.09±82.87

Data expressed as mean±SD or median (interquartile range). **Abbreviations:** 6MWD: six-minute walk distance; SpO₂= oxygen saturation; VE= pulmonary ventilation, MMV=maximal voluntary ventilation; VO₂= oxygen consumption; MET= metabolic equivalent. Two-way repeated measures analysis of variance: *main effect of time $p<0.05$.

- Complaints

There was no statistically significant interaction between the training and time and no main effect of time and intervention on the mMRC scale (Table 3S).

There was no statistically significant interaction between the training and time for the LCADL and all domains. There was a statistically significant effect of time on the LCADL physical domain ($F=9.644$, $p=0.005$, partial $\eta^2=0.305$, observed power=0.843), total score ($F=7.260$, $p=0.013$, partial $\eta^2=0.248$, observed power=0.731), and percentage of total ($F=4.802$, $p=0.039$, partial $\eta^2=0.179$, observed power=0.554) (Tables 3 and 3S).

The main effect of time showed a statistically significant difference in mean dyspnea during ADL simulation at the different time points ($F=9.829$, $p=0.005$, partial $\eta^2=0.309$, observed power=0.992) (Tables 3 and 3S)

- *Quality of life*

There was a statistically significant interaction between the intervention and time for SGRQ symptoms ($F=4.232$, $p=0.050$, partial $\eta^2=0.161$, observed power=0.502). The main effect of time was statistically significant for SGRQ symptoms and furthermore, there was a statistically significant effect of time on SGRQ symptoms for the LL/HR group ($F=16.372$, $p=0.002$, partial $\eta^2=0.577$, observed power=0.960) (Tables 3 and 3S).

Table 3. Complaints and Quality of life of COPD patients randomly assigned to low-load/high-repetition (LL/HR) and high-load/low-repetition (HL/LR) pre- and post-exercise training

	LL/HR (n=13)		HL/LR (n= 11)	
	Pre-	Post-	Pre-	Post-
Complaints				
mMRC	1 (1-3)	1 (1-2)	2 (1-3)	1 (1-2)
LCADL				
- <i>Self-care score</i>	5.53±2.18	4.30±1.97	5.09±1.13	5±1.09
- <i>Domestic score</i>	4.25±3.33	3.75±3.44	4.18±2.82	3.09±3.14
- <i>Physical score</i>	3.91±1.16	3.16±0.83*	4±1.18	3.36±1.12*
- <i>Leisure score</i>	3.91±1.24	3.58±0.9	3.9±2.11	3.36±0.54
- <i>Total score</i>	17.61±4.78	15.16±5.06*	17.18±5.25	14.81±4.68*
- <i>%Total score</i>	29.36±9.03	27.36±9.41*	29.01±9.38	25.36±4.08*
ADL simulation				
- <i>Dyspnea, BORG</i>	1 (0.25-3)	0.5 (0-2.5)*	1 (1-3)	1 (0-2)*
Quality of life				
SGRQ				
- <i>Symptom score</i>	40.27±20.05	26.43±18.24*†	33.40±17.94	30.97±16.12*
- <i>Activity score</i>	48.30±24.52	49.51±27.24	58.49±22.59	53.91±15.29
- <i>Impact score</i>	19.76±12.08	21.36±14.11	31.19±19.54	23.36±18.68
- <i>Total score</i>	34.70±17.47	30.73±17.45	39.83±19.09	33.88±15.76

Data expressed as mean±SD or median (Q1-Q3). **Abbreviations:** mMRC= medical research council dyspnea grade; LCADL= London Chest Activity of Daily Living Scale; SGRQ= Saint George's Respiratory Questionnaire. Two-way repeated measures analysis of variance= $p<0.05$: *effect of time; †effect of time X training.

Responsiveness to the treatment

In figure 2 the percentage of patients who achieved MID values after the training for the 6MWD, mMRC, LCADL, and SGRQ can be observed. No differences between the percentage of patients who achieved MID/MDC values post-intervention were found comparing LL/HR and HL/LR training ($p>0.05$).

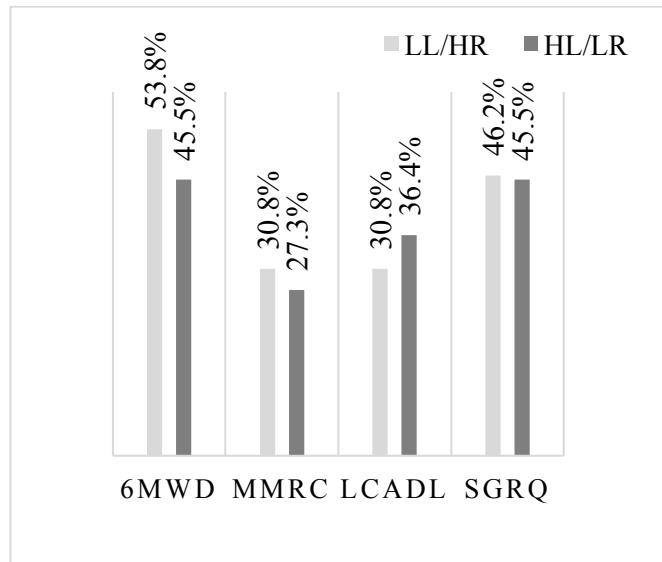


Figure 2. Percentage of patients who achieved MID - minimal importance difference or MDC - minimal detectable changes
Abbreviations: 6MWD= six-minute walk distance; mMRC= medical research council dyspnea grade; LCADL= London Chest Activity of Daily Living Scale; SGRQ= Saint George's Respiratory Questionnaire. No significance difference by Chi-square test.

Discussion

This study provided three important findings regarding health status after two different intensities of resistance training: first, both intensities improved dyspnea during ADL and LCADL by the same magnitude, followed by an increase in exercise capacity and muscle strength; second, an interaction between intervention and time was observed in the symptom domain of SGRQ – which reflects quality of life – with a greater effect of time in the LL/HR group, and third, the percentage of patients who achieved the MID/MDC for the LCADL, mMRC, 6MWD, and SGRQ was similar in both training groups.

This study contributes to the existing literature as it examines the responsiveness of health status, assessed by ADL performance and complaints followed by increases in exercise tolerance and muscle strength to different intensities of resistance training. As described by Vercoulen⁷, the health-status sub-domain classification is an important characteristic as there is a relatively independent relation between the domains. Furthermore, the sub-domain classifications converge the often theoretical notions of the main domains defined in the literature into much more concrete and detailed definitions⁷.

Patients in the present study performed specific aerobic training on a cycle ergometer and at two different intensities of resistance training. The resistance training encompassed three different exercises: one for the lower limbs, which are known to be the most impaired muscle group in COPD patients³², and two exercises for the upper limbs, the most commonly used muscle group for ADLs in COPD patients. We observed that all patients, at both intensities of resistance training tolerated the loads imposed in all sessions with no reported adverse events. Furthermore, we observed that for both intensities of training, the proportions of patients who achieved and did not achieve the values of MID/MDC for the assessed outcomes were similar.

To our knowledge, the present study is the first to assess physiological functioning during ADL simulation – such as dyspnea, oxygen consumption, and ventilatory demand and efficiency - pre- and post- two intensities of resistance training combined with aerobic training.

In the present study, after 36 sessions of two different resistance intensities, a significant improvement in dyspnea was evident during ADL simulation. The reduction in dyspnea may have a relation with the increase in muscle strength and endurance which could contribute to greater sustainability of task performance and lower levels of perceived breathlessness, and clinically, present an association with improved functional performance⁵⁵. Costi and colleagues¹⁵ compared patients who performed 3-weeks of specific training for the lower extremities and general exercise with those who performed upper extremity exercise training. Patients who performed the latter presented a greater decrease in dyspnea during ADL simulation as well as a reduction in LCADL, corroborating our findings, as our training encompassed both upper and lower limb training and led to improvements in dyspnea and LCADL.

A meta-analysis by O'Shea and colleagues³⁴ showed a positive effect of progressive resistance exercise on stair-climbing speed, time during the sit-to-stand test, and time in upper limb-lifting activities and mobility, activities that reflect daily activities. Velloso and colleagues³⁵ assessed improvements in several ADL performances, assessing oxygen saturation, heart rate, and dyspnea, after 8-weeks of aerobic training on a treadmill and exercises using diagonal movements. The authors reported a decrease in dyspnea only for the ADL teeth brushing, with no changes for other ADL outcomes. Panton and colleagues³⁶ reported a reduction in the time to perform some ADLs but no changes in dyspnea after concomitant aerobic and resistance training.

However, unexpected results were found regarding the ADL ventilatory and metabolic variables, with no differences in ventilatory demand, ventilatory efficiency, or oxygen consumption post-training. It has long been observed that patients with COPD often experience only moderate improvements in aerobic capacity after completion of an exercise training program. The increase in oxygen consumption is nearly 10-20% of baseline³⁷, which may be due to respiratory limitation to exercise in these patients and the inability of lung tissue to remodel itself compared to cardiac tissue³⁸. Therefore, the majority of training adaptations achieved predominantly take place in the peripheral muscle and different physiological effects as a result of different training intensities might have a similar impact on patients with COPD. It is possible the impact on the ADL outcome would be best achieved by designing specific ADL training activities, with more functional exercises, regardless of resistance training using equipment. Despite the lack of changes in ADL metabolic and ventilatory parameters, when we look specifically at ventilatory efficiency, we can see that in the LL/HR there was an improvement, while a decrease in values was noted in the HL/LR.

Exercise capacity - assessed by the 6MWD - presented an increase after both intensities of resistance training. Despite the percentages of patients who achieved the MID value being statistically equal for the 6MWD, the observed variation between pre- and post-exercise was higher for those patients who performed the LL/HR. This finding is in line with the results described by Nyberg and colleagues³⁹, who found that functional capacity seems to be more closely related to limb muscle endurance than to limb muscle strength.

In the present study, although we did not assess muscle endurance directly, the LL/HR training focused on muscle endurance gains and increases in peripheral muscle strength can also improve endurance⁴⁰. However, when assessing muscle strength, HL/LR did not confer

additional benefits to muscle strength, with both groups presenting an improvement after training. This finding can be explained by the principle of overload, which involves increasing the exercise dosage over time to maximize gains in muscle strength and endurance⁴¹ as in our training protocols, leading to an increase in muscle strength in both intensities of training. Moreover, O'Shea and colleagues⁴² also reported an increase in muscle strength after a low-intensity home based intervention. As both muscle strength and endurance are required during ADLs, increases might lead to less dyspnea during these activities.

Conversely, Probst and colleague⁴³, reported a significant increase in muscle strength after high-intensity whole-body endurance compared to a low-intensity calisthenics-and-breathing program. This contradictory result may to some extent be explained not only by the different methods used to assess muscle strength but also different scenarios of resistance training performance. Probst and colleagues⁴³ assessed muscle strength using a 1RM test performed in the same machine used to perform the high-intensity training. In our study, we assessed muscle strength by a hand-held dynamometer, which assesses isometric muscle contraction. Indeed, the specificity of the training is very important for the outcomes, and as our resistance training was performed using isotonic movements this might explain the improvement in both training intensities.

We found an improvement in complaints after both intensities of resistance training. An improvement in the LCADL scale after the exercise training is noteworthy, as COPD patients often reduce their ADLs unconsciously in order to limit the intensity of exertional dyspnea⁴⁴. Reduction in performing ADLs leads to sedentary behavior which further increases dyspnea. The effects of an intervention on ADLs should be considered as an essential component of treatment goals⁴⁵ and more than that, proxies (loved ones) should always be involved, as well as patients to help identify problematic ADLs in patients⁴⁶, allowing selection of the most appropriate treatment. We did not find an improvement in mMRC, which might have occurred as the LCADL is a much more comprehensive tool than the mMRC, and the ADL assessed in the present study is much more similar to the ADL assessed by the LCADL.

Concerning quality of life, a superior effect of LL/HR on symptom domains of SGRQ was noted in the present study, with no difference in the other two domains or total SGRQ score after both training intensities. Patients who develop quadriceps contractile fatigue during exercise training demonstrate a greater training effect in terms of functional capacity and HHQoL, as described by Burtin and colleagues⁴⁷. As we did not measure this in our study,

we cannot infer this relationship; however it could have interfered in our findings regarding the quality of life. Kovelis and colleagues⁴⁸ reported a decrease in SGRQ total score after a 12-week training program, however, before training, patients presented a greater score (SRGQtotal: 53[41-65]) compared with our patients. This may be a justification for the lack of significant changes in SGRQ found in the present study.

Nevertheless, improvement in SGRQ symptoms, dyspnea in the ADL simulation, and LCADL are still noteworthy, since presenting fewer symptoms and better function in ADLs is what the patient expects after exercise training⁴⁹.

The magnitude of response to exercise training is highly variable in COPD, with some patients presenting little or no benefit⁵⁰. Despite the lack of statistical difference in the SGRQ total score after both intensities of training, we observed that at least 45% of patients achieved the MID values described for this variable. It is possible the low number of participants in each training group justifies this finding, due to the drop-outs after the randomization.

One possible limitation of this study is the failure to achieve any effect on one of our primary outcomes - ADL ventilatory demand and efficiency. This may be explained by the drop-out rate which led to a small number of participants in each group, and also by the specificity of the exercise training. Second, we did not include a muscle endurance test, which would have provided straightforward information about muscle endurance, however some ADLs which indirectly refer to the muscle's ability to sustain or repeat a specific task over time were assessed, corresponding to muscle endurance⁵¹.

However, the implication for clinical practice is that both low and high load resistance training can be used, and the specificity of the training protocol should be taken into account, considering the improvements in outcomes required by the patient to have great performance in daily living, which will be reflected in an improvement in quality of life. Future studies with a larger and more heterogeneous group of COPD patients are necessary to deepen the understanding on the effects of resistance training intensities and specificity in ADL performance, although, we strongly recommend that prescription be targeted to the individual needs.

Conclusion

In conclusion, our study demonstrates an equivalent improvement in ADL dyspnea and LCADL followed by improvements in exercise capacity and muscle strength after both LL/HR and HL/LR. No differences were found in oxygen consumption, ventilatory demand, or efficiency after either intensity of resistance training as well as a superior effect of LL/HR training in the symptoms domain of the SGRQ.

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Chapter 4

Short and long-term effects of acute exacerbations on health status beyond pulmonary function in patients with COPD - a systematic review

In this chapter, we will describe the aim, methods, results and discussion from the manuscript titled Short and long-term effects of acute exacerbations on health status beyond pulmonary function in patients with COPD - a systematic review, has not been submitted yet.

The aim of this study is to summarize the existing evidence on the impact of exacerbations of COPD on health status beyond pulmonary function in a systematic manner. This will provide clinicians and researchers with a comprehensive and nuanced view on the detrimental impact of exacerbations in this patient population.

Methods

Database and search strategy

Two researchers (MSBG and CB) performed an electronic literature search of PubMed from inception until September 2017. The following search strategy was used: (COPD [title/abstract] OR chronic obstructive pulmonary disease [MeSH]) AND (hospital*[title] OR exacerbation [title/abstract]).

Title screening was performed by a single researcher (MSBG or CB) in a conservative way, only excluding studies that clearly did not fulfill the criteria. Abstract screening and consequent full-text screening were performed independently by two researchers (MSBG and CB). Results were compared, and a consensus-based decision was taken after discussing possible discrepancies.

Selection criteria

Only prospective studies that performed at least one type of assessment of health status were included. Based on the sub classification of health status in COPD proposed by Vercoulen et al.¹, we included measures of physiological functioning (exercise tolerance, muscle function and body composition), complaints (subjective complaints, (expected) dyspnea, emotions, fatigue), functional impairment (subjective impairment, behavioral impairment, actual physical activity) and quality of life (QoL; general QoL, health-related quality of life, satisfaction, relations). Measures of pulmonary function and dyspnea symptoms outside the context of daily life activities (e.g. trials investigating resting dyspnea throughout an acute exacerbation) were not included.

Assessment needed to be done at baseline (in a stable disease phase) and after a period of follow-up. This could be immediately after or during follow-up of a single exacerbation. Alternatively, patients could be followed over a longer period of time with the

onset of exacerbations during the follow-up period being recorded (e.g. to compare changes in functional status in frequent exacerbators vs. non-frequent exacerbators)

Only studies published in English were included.

Data extraction

Information on study design and timing of assessment, sample size, baseline characteristics (age, gender, anthropometrics, forced expiratory volume in one second (FEV₁)), the measure of functional status, used definition of (frequent) exacerbations and main results regarding functional status was extracted. We separated studies that investigated the effects of a single exacerbation and studies that investigated the influence of frequency of exacerbations over a follow-up period.

Quality assessment

Quality of the studies was assessed using the “Quality Assessment Tool for Observational Cohort and Cross-Sectional Study” (QAT) from National Institutes of Health – NIH² (see attachment B). This is a 14-item checklist which scores articles as poor, fair or good, based on methodological quality. This assessment was done by two researchers (MSBG and JDB) independently. In case of disagreement, the researchers discussed the article in an effort to reach consensus. If deemed necessary, the article was forwarded to a third author (CB) to make a final decision.

Results

Search results

We identified 5962 articles using our search strategy. During title screening, 5871 articles were excluded, leaving 91 articles for abstract screening. During abstract screening, 62 articles were excluded and 29 full-text articles were screened. In the end, 17 articles fulfilled all inclusion criteria and were included in our review. The screening process is visualized in a flow chart (Figure 1).

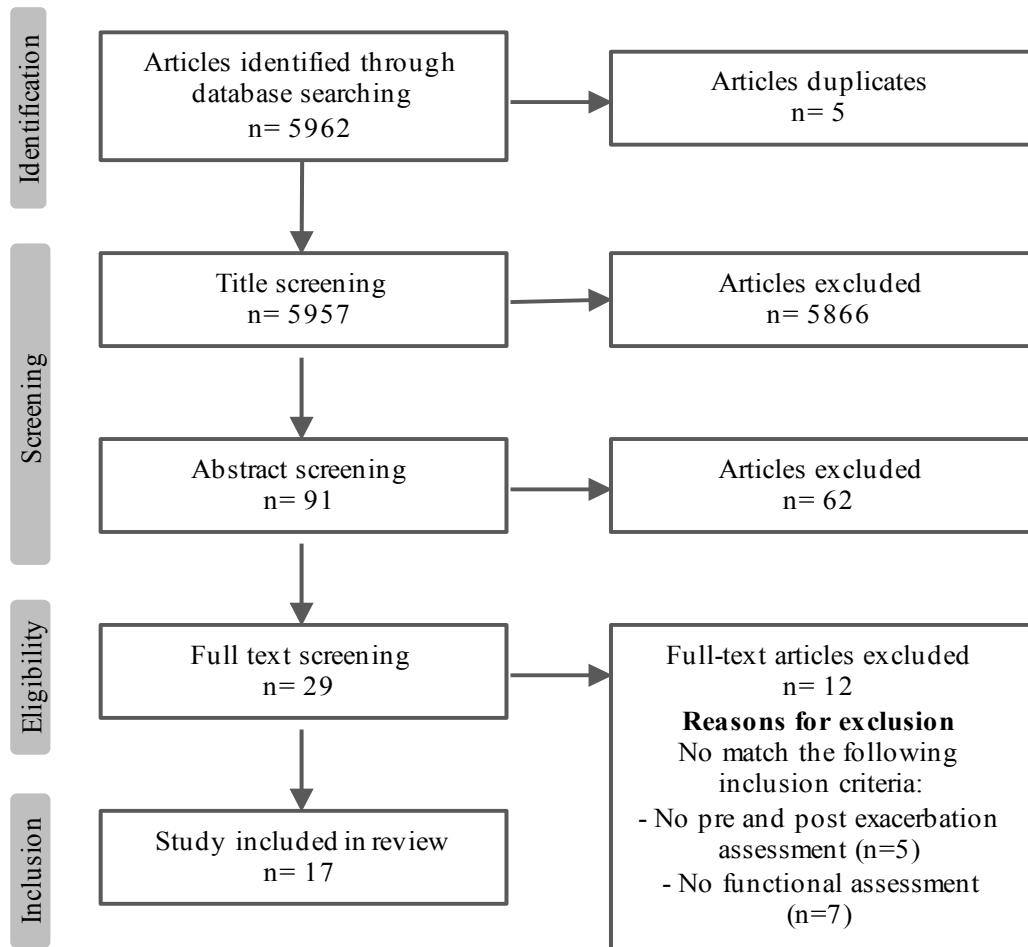


Figure 1. Study flowchart showing the screening of the articles to final inclusion

Quality assessment

The quality assessment is summarized in Table 1. The research question was clearly specified and defined in all of the included studies. The study population was not clearly defined in two studies^{3,4}. The participation rate of the eligible patients was reported in five of the seventeen studies⁵⁻⁹. One study¹⁰ did not specify the inclusion and exclusion criteria. One study reported a sample size calculation¹¹. The exposures of interest, i.e. exacerbation, were measured prior to the outcomes being measured in nine studies^{5-8,10-14}. So, in some studies the exacerbation was collected by patient report during the follow-up, but actually exacerbation occurs before the outcome be measure. We did not consider as a bias if the study scored “no” to this question.

The timeframe to investigate an association between the exacerbation and the outcome was sufficient in all of the included articles. Different levels of the exposure were taken into account in eight studies^{9,11-13,15-18}.

One study did not clearly define exacerbation¹⁰. The outcome measures were clearly defined, valid, reliable and implemented consistently in all of the included studies. One study reported blinding of the outcome assessors to the exposure status of the patients⁷, which is probably because the study design made it difficult in order to do. Loss to follow-up after baseline was 20% or less in four studies^{4,7,16,19}, and we should consider the follow-up period had a great variance between the studies. Nine of the seventeen included studies measured potential confounding variables and adjusted statistically for their impact^{4,7,8,12,13,15,17,18,20}.

We classified the study of Rubinsztajn and colleagues¹⁰ as poor because they did not specify the study population, the inclusion and exclusion criteria and the exposure was not clearly defined.

Table 1. Result of the “Quality Assessment Tool for Observational Cohort and Cross-Sectional Study”

QAT Question	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Quality rating
Alahmari et al., 2014	Y	Y	Y	Y	N	Y	Y	NA	Y	N	Y	NA	N	N	Fair
Alahmari et al., 2016	Y	Y	N	Y	N	Y	Y	N	Y	N	Y	N	NR	N	Fair
Anzueto, Leimer & Kersten, 2009	Y	Y	NR	Y	N	N	Y	Y	Y	Y	Y	N	NA	Y	Good
Cote et al., 2007	Y	Y	NR	Y	N	N	Y	Y	Y	Y	Y	N	Y	N	Good
Donaldson et al., 2005	Y	Y	NR	Y	N	Y	Y	Y	Y	CD	Y	NA	N	Y	Good
Dreyse et al., 2015	Y	N	NR	CD	N	N	Y	NA	Y	Y	Y	N	Y	Y	Good
Ehsan et al., 2013	Y	Y	Y	Y	N	Y	Y	NA	Y	Y	Y	Y	Y	Y	Good
Esteban et al., 2009	Y	Y	NR	Y	N	Y	Y	Y	Y	Y	Y	N	N	Y	Good
Ferrari et al., 2011	Y	Y	Y	Y	N	Y	Y	NA	Y	Y	Y	N	N	Y	Good
Hopkinson et al., 2007	Y	Y	NR	Y	N	N	Y	NA	Y	N	Y	N	N	Y	Fair
Kardos et al., 2017	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	N	N	N	Good
Llor et al., 2008	Y	Y	NR	Y	Y	Y	Y	Y	Y	Y	Y	N	N	N	Good
Melbye et al., 2016	Y	Y	N	Y	N	Y	Y	N	Y	N	Y	NA	Y	N	Fair
Nishimura et al., 2009	Y	Y	NR	Y	N	N	Y	Y	Y	Y	Y	N	NR	Y	Good
Rubinsztajn et al., 2016	Y	N	NR	N	N	Y	Y	NA	N	Y	Y	N	N	N	Poor
Spencer et al., 2004	Y	Y	NR	Y	N	N	Y	Y	Y	Y	Y	N	NR	Y	Good
Steele et al., 2010	Y	Y	NR	Y	N	Y	Y	NA	Y	Y	Y	N	N	N	Fair

Abbreviations: Y= yes; N= no; NR=not reported; NA=not available; CD= cannot determine

Health status assessment beyond the lungs

Physiological functioning beyond the lungs were assessed in eight studies: five studies used the 6-minute walking distance (6MWD)^{4,6,8,14,16}. Two studies assessed quadriceps maximum voluntary contraction (QMVC)^{6,20} and one study assessed fat-free mass (FFM)²⁰.

Complaints were assessed in nine studies: four studies used mMRC^{4,8,10,16}, one study used the Clinical COPD Questionnaire (CCQ)¹⁹, one study used COPD Assessment test (CAT)⁹, one used Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F)⁶, one the Baseline Dyspnea index (BDI) and Transition Dyspnea Index (TDI)¹⁵, and one the Seattle Obstructive Disease Questionnaire (SOLDQ)¹⁴.

Functional impairment was assessed in six studies: concerning physical activity behavior, three studies used the physical activity level (PAL)^{6,7,14}, two quantified the time spent outdoor based on a diary^{5,12}, one measured daily step count⁵ and one study used the Walking Self-Efficacy²¹.

Quality of life was assessed in 13 studies: nine studies used the Saint George's Respiratory Questionnaire (SGRQ)^{4,8,10,11,13,15,17,18,20}, while two studies used the Chronic Respiratory Disease Questionnaire (CRQ)^{4,17} and two studies used the SF-36^{13,21}.

Effect of a single exacerbation on health status

Six studies assessed the direct effect of a single AECOPD on health status. Details of these studies are provided in table 2.

- Physiological functioning

Alahmari et al.⁶ reported a significant reduction of 49 meters in 6MWT in the first three days after the onset of a moderate AECOPD. After one week the values were almost back to the pre-AECOPD status. No differences in 6MWD were found when they divided patients in frequent and infrequent exacerbators in the preceding year. QMVC was significantly reduced by 8.9% and 10.7%, three and seven days after the onset of exacerbation symptoms respectively. Cote et al.¹⁶ reported a significant 72m (20%) decrease in 6MWD assessed within 48 hours of symptom onset related to a moderate AECOPD. This decrease was maintained up to two years of follow-up, with no significant difference between patients that did or did not experience new exacerbations during this period.

- Complaints

Melbye et al.¹⁹ measured CCQ at baseline and within three days after the onset of a self-reported AECOPD. When subdividing patients with (34% of patients) and without a drop in FEV₁ exceeding 10% or 200ml compared to the stable situation, absolute CCQ score increased in both groups (no statistics performed) and no differences were found between groups. Alahmari et al.⁶ reported a significant reduction in FACIT-F score of 13.8% at the onset of a moderate exacerbation and 5.4% at day three compared to the stable situation. Cote et al.¹⁶ found a 0.47 point (20%) increase in MMRC dyspnea scale assessed within 48 hours of symptom onset related to a moderate AECOPD. This decrease only partially recovered during up to two years of follow-up; patients who experienced new exacerbations during the follow-up period had a more pronounced change in MMRC.

- *Functional Impairment*

Alahmari et al.⁵ reported a reduction of 480 steps per day during a week starting from exacerbation onset compared to a stable week (on average 4154 vs 3673 steps per day respectively) in non-hospitalized patients. On average, patients needed 11 days to return to baseline levels, but patients with a larger decrease in daily step count needed more time to recover to baseline. Self-reported time spent outdoors and the percentage of days on which patient went outdoors was not different when comparing the exacerbation and baseline period. Ehsan et al.⁷ reported a significant reduction of 26 minutes (17%) in the amount of the time spent in “higher level physical activity” based on vector magnitude units during exacerbation days compared to stable days. Moreover, a gradual increase in activity over the subsequent weeks was observed; pre-exacerbation period levels were approached after three weeks. Donaldson et al.¹² reported that during a stable baseline period, patients stayed at home all day for on average 2.1 days/week. This number rose to 2.7 days/week in the post-exacerbation period (day 1 to 35; the vast majority being mild and moderate exacerbations).

Table 2. Effect of a single exacerbation on health status in patients with COPD						
Author(s), year	Study design/ Time of assessment	Sample size	Patient characteristics baseline	Functional capacity assessment instrument	How to diagnosed an exacerbation	Main results
Alahmari et al., 2014	<p>Observational prospective study</p> <p>Were pedometer for a minimum of 35 days: Average value over 7-day baseline period which started 2 weeks before onset with the average value over a 7 days exacerbation period starting on the day of exacerbation onset.</p> <p>Recovery was determining as the day after exacerbation onset when a 3-day moving average of a parameter matched or exceeded its baseline value</p>	<p>n= 73 COPD patients Male: n= 51 Female: n= 22</p> <p>Divided in infrequent/frequent exacerbators based in the 12 moths preceding the start of the study</p> <p>- infrequent exacerbators (0-1 exacerbation): n= 33</p> <p>- frequent exacerbators (>2 exacerbation): n= 40</p>	<p>Age, y= 71.1±8.7 FEV₁,%= 52.9±16.5 BMI, kg/m²= 26.8±5.6</p> <p>infrequent/frequent exacerbators: baseline characteristics NA</p>	<p>Daily step-counts (step/day)</p> <p>Time outdoors (hours/day)</p> <p>Percentage of days on which patients went outdoors (%)</p>	<p>Recorded in a diary and defined as an increase in respiratory symptoms for 2 consecutive days, with at least one major symptom (dyspnea, sputum purulence our sputum volume) plus either another major or a minor symptom (wheeze, cold, sore throat, and cough)</p>	<p>All 73 patients</p> <p>Daily step-counts (step/day) Stable state: 4154±2586 Exacerbation: 3673±2258 Change for baseline: ↓ 480±1408, p=0.045 Days to return to baseline levels: 11(IQR 8.17)</p> <p>Time outdoors (hours/day) Stable state: 3.4±1.8 Exacerbation: 3.2±1.8 Change for baseline: ↓ 0.1±1.1, p=0.51 Days to return to baseline levels: 1.4(IQR 0.3-5.3)</p> <p>Percentage of days on which patients went outdoors (%) Stable state: 84.4±24.2 Exacerbation: 79.6±26.1 Change for baseline: ↓ 4.8±§8, p=0.13</p> <p>Days to return to baseline levels:</p>

						<p>11(IQR 8.17)</p> <p><i>Divided in frequent and infrequent exacerbators</i></p> <p>Daily-step count decline</p> <p>- Infrequent exacerbators (n=33): 338 steps/year [95% CI: -504 to -170]</p> <p>- Frequent exacerbators (n=40): 208 steps/year [95% CI: -867 to -549%], p=0.002.</p>
Alahmari et al., 2016	<p>Observational prospectively study</p> <p>- Baseline</p> <p>- At exacerbation (0-d)</p> <p>- 3 and 7 days post exacerbation</p>	<p>Performed 2 protocols</p> <p>Protocol 1 (PAL + 6MWT):</p> <p>PAL: n=50 patients and 6MWT: n=44 patients</p> <p>Protocol 2 (QMVC): n=47 patients (19 of whom had performed protocol 1)</p>	<p>Protocol 1:</p> <p>PAL:</p> <p>Age, y= 72.9±8.2</p> <p>FEV₁,%=50.7±15.1</p> <p>BMI, kg/m²= 26.6±5.6</p> <p>mMRC= NA</p> <p>6MWD:</p> <p>Age, y= 73.3±8.3</p> <p>FEV₁,%= 50.2±15.8</p> <p>BMI, kg/m²= 26.6±5.6</p> <p>Protocol 2:</p> <p>Age, y= 72.4±7.8</p> <p>FEV₁,%=50.1±17.2</p>	<p>PAL, 6MWT</p> <p>Quadriceps maximum voluntary contraction (QMVC) and Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F)</p>	<p>Defined as an increase in respiratory symptoms for 2 consecutive days, with at least one major symptom (wheeze, cold, sore throat or cough)</p>	<p>Energy expenditure >2.5METS</p> <p>week 1= 2.18±0.23 h.day⁻¹</p> <p>week 2= 1.98±0.22 h.day⁻¹, p=0.009</p> <p>6MWD, change for baseline</p> <p>Baseline: 422m (337-550m)</p> <p>3-d= 373m (265-450m), change for baseline: ↓49m (13.1%), p=0.001</p> <p>7-d= 415m (290-490m), change for baseline: ↓7m (1.65%), p=0.103</p> <p>QMCV</p> <p>Baseline: 32.6±2.7kg</p> <p>3-d= 29.7±2.5kg, change for baseline: ↓ 2.9kg (8.9%) , p=0.026</p> <p>7-d= 29.1±2.8kg, change for baseline: ↓ 3.5kg (10.73%), p=0.019</p>

SHORT AND LONG-TERM EFFECTS OF AECOPD ON HEALTH STATUS

			BMI, kg/m ² = 25.9±5.6			<p>FACIT-F level 0-d= 31±1.7, change for baseline ↓ 5 (13.8%), p<0.001 3-d= 37±1.4, change for baseline ↓ 2 (5.4%), p=0.037</p> <p><i>Also divided the patients in frequent exacerbators (12-months previous), GOLD grade and who had ever previously attend or not in PR</i></p> <p>Energy expenditure >2.5METS, difference between week 1 and 2 - infrequent exacerbators: ↓0.10±0.09 h.day⁻¹ - frequent exacerbators: ↓0.40±0.11 h.day⁻¹ p=0.048</p> <p>- never attended PR: ↓0.14±0.129 h.day⁻¹ - ever attended PR: ↓0.06±0.07 h.day⁻¹ p=0.016</p> <p>6MWD, difference between week 1 and 2 - GOLD 1-2: ↓24.1±13.8 m - GOLD 3-4: ↓81±21.9m p=0.034</p> <p>- never attended PR: ↓114±32.2m</p>
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SHORT AND LONG-TERM EFFECTS OF AECOPD ON HEALTH STATUS

						- ever attended PR: $\downarrow 35.0 \pm 14.1$ m p=0.013
Cote et al., 2007	Observational prospective study Baseline Acute: immediately after exacerbation 6-months, 1 and 2-years after exacerbation	Non exacerbator: n= 75 Male: n=72 Female: n=3 COPD exacerbators patients: n= 130 Male: n=122 Female: n= 8 Divided in: Single exacerbators: n=48 Male: n=46 Female: n=2 Frequent exacerbators: n= 82 Male: n=76 Female: n=6	- Non exacerbator Age, y= 67 ± 9 FEV ₁ ,% = 48.5 ± 16 BMI, kg/m ² = 28 ± 6.27 - Single exacerbators: Age, y= 65 ± 9 FEV ₁ ,% = 42.6 ± 15.54 BMI, kg/m ² = 27.39 ± 6.17 - Frequent exacerbators: Age, y= 68 ± 9 FEV ₁ ,% = 37.68 ± 14.3 BMI, kg/m ² = 27.42 ± 5.84	6MWT	Defined as an event characterizes by a sustained worsening of respiratory symptoms for at least 2 days, requiring the following: a visit to a doctor or the emergency department; and treatment with antibiotics or systemic steroids or both, but no necessitating a hospitalization	Changes during the exacerbation and after the initial episode compared to baseline Change from baseline - COPD exacerbators patients: 6MWD Acute: $\downarrow 72$ m (20.4%) - Single exacerbators: 6MWD Acute: $\downarrow 77$ m (20%), p=0.002 mMRC Acute: $\uparrow 0.41$ pt (19.2%), p=0.04 - Frequent exacerbators: 6MWD Acute: $\downarrow 69$ m (21%), p=0.0002 mMRC Acute: $\uparrow 0.51$ pt (21.5%), p=0.0005 Values of SD not provided

SHORT AND LONG-TERM EFFECTS OF AECOPD ON HEALTH STATUS

<p>Donaldson et al., 2005</p>	<p>Observational prospective study</p> <p>Baseline: 8-14 days preceding exacerbation onset</p> <p>Day of the exacerbation onset</p> <p>Recovery: 3-day moving average of the parameter to equal or exceed baseline within a period of 35 days</p>	<p>COPD patients: n= 147</p> <p>Male: n= 101</p> <p>Female: n= 46</p>	<p>Age, y= 67.6±7.6</p> <p>FEV₁,%=40.9±15.7</p> <p>BMI, kg/m²= NA</p>	<p>Time spent outdoor: - percentage of the day remains indoors - days/week</p>	<p>Recorded in a diary and defined as an increase in respiratory symptoms for 2 consecutive days, with at least one major symptom (dyspnea, sputum purulence our sputum volume) plus either another major or a minor symptom (wheeze, cold, sore throat, and cough)</p>	<p>Percentage of the days spent indoor</p> <p>Day of exacerbation onset: ↑ 10.3% (552 of 1,244 days vs 3,957 of 9,663 days), p=0.021</p> <p>Recovery: ↑ 5.6% (17,032 of 42,864 days vs 3,957 of 9.663 days), p=0.024</p> <p>Days/week</p> <p>Post exacerbation period compared to baseline: ↑ 0.4 days/week (IQR, 0.03 to 0.82 days/week), p=0.001</p>
<p>Ehsan et al., 2013</p>	<p>Observational longitudinal study</p> <p>6 months with return visits monthly (if no exacerbation occurred)</p> <p>For up to 4 weeks after a documented clinical exacerbation</p>	<p>n= 17 COPD patients</p> <p>Male: n= 9</p> <p>Female: n= 8</p>	<p>Age, y= 63±12</p> <p>FEV₁,%=52±20</p> <p>BMI, kg/m²= 25±5</p>	<p>PAL: Minutes per day in higher level activities</p>	<p>Used the 14-item Exacerbations of Chronic Obstructive Pulmonary Disease Tool (EXACT) to capture symptom-defined exacerbations, it is a paper based diary and the scores range from 0 to 100. Increases > 9 points sustained for 3 days or 12 points sustained for 2 days from baseline indicate the onset of an exacerbation and the decline in the same magnitude indicated recovery</p>	<p>Time in higher level activities</p> <p>Non-exacerbation days: 157±14 minutes</p> <p>Exacerbation days: 131±13 minutes</p> <p>Change after exacerbation ↓ 26 min/day (17%), p< 0.0001</p>

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					from that exacerbation	
Melbye et al., 2016	Observational prospectively study - Baseline - 2-3 days post exacerbation	n= 88 - n=40 Asthma patients Male: n=16(40%) Female: n= 24(60%) - n= 48 Asthma + COPD patients Male: n=18(38%) Female: n= 30(68%) Divided the 88 patients concerning the drop in FEV ₁ from baseline of 10% and ≥ 200ml, calling “no” or “yes” No: n=58 Yes: n=30	For all patients Age, y= 63 (SD NA) Asthma patients Age= NA FEV ₁ , %=87.5 (SD NA) BMI, kg/m ² = NA Asthma + COPD patients Age= NA FEV ₁ , %=61.2 (SD NA) BMI, kg/m ² = NA	Clinical COPD Questionnaire (CCQ)	Defined by prescription of oral steroids and/or antibiotics or hospitalization	CCQ respiratory score , change for baseline No= ↑ 1.25 (SD NA) Yes= ↑ 1.0 (SD NA) p=0.6 CCQ total score No= ↑ 1.05 (SD NA) Yes= ↑ 0.7 (SD NA) p=0.9
Abbreviations: 6MWD= six-minute walking distance; 6MWT= six-minute walking test; BMI= body mass index; BODE= body mass, obstruction, dyspnea and exercise capacity; CI= confidence interval FEV ₁ = forced expiratory volume in the first second; IQR= inter quartile range; MET= metabolic rate mMRC= Medical Research Council scale for dyspnea; NA= not available; PAL= Physical activity level; PR= pulmonary rehabilitation; SD= standard deviation; SF-36= 36-item short form survey.						

Influence of (repeated) exacerbations on changes in functional status over time

Twelve studies assessed the influence of exacerbation occurrence or exacerbation frequency on longitudinal changes over time. Details of the studies are provided in table 3.

- Physiological functioning

Dreyse et al.⁴ showed that frequent exacerbators (two or more per year) during a 2-year follow up period consistently had a lower 6MWD during repeated six-month assessment. In patients who experienced a moderate exacerbation, Cote et al.¹⁶ reported no difference in 6MWD decline in patients that did or did not experience new exacerbations during a two-year follow-up period.

Concerning changes in muscle strength and fat free mass, Hopkinson et al.²⁰ found a significant association between having frequent exacerbations (two or more per year) and the decline of FFM but not with decline in quadriceps muscle strength.

Steele et al.¹⁴ compared completers of an eight-week pulmonary rehabilitation program who did or did not experience an exacerbation throughout the rehabilitation period. Patients with an exacerbation showed a significant increase of 64 meters in 6MWD, which was unexpectedly but significantly higher than the increase in patients without exacerbations.

- Complaints

Kardos et al.⁹ assessed the proportion of patients with a clinically relevant improvement (two or more units) or worsening from baseline in CAT score during a one and two-year follow up period. They reported that exacerbation rate was significantly lower in patients with a sustained improvement than those with a sustained worsening (0.32 vs 0.52 annual exacerbations over the two years follow up respectively). They also suggested that patients who were classified as GOLD B had the least change in disease severity over the two years. Dreyse et al.⁴ reported that frequent exacerbators had higher mMRC score than non-frequent exacerbators.

- Quality of life

Dreyse et al.⁴ showed that frequent exacerbators (two or more per year) during a two-year follow-up period had consistently higher SQRQ scores and lower CRQ scores than

non-frequent exacerbators, as measured every six months during follow-up. Rubinsztajn et al.¹⁰ reported that patients with two or more exacerbations per year during a two year follow-up period had significantly higher values for SGRQ symptoms, activity, impact and total score compared those with 0-1 exacerbations/year.

In the study of Ferrari et al.⁸ 75% of 95 patients had at least one exacerbation and these patients presented with a higher SGRQ total score (44 units) compared with those without exacerbation (21 units) after a period of three years follow up. They also reported that number of exacerbations during follow-up, mMRC and FEV₁ were independent predictors of health status at three years follow-up.

Nishimura et al.¹⁷ reported that both patients with or without exacerbations presented a statistically significant decline in different aspects of health status over six months, as assessed with CRQ and SGRQ. Patients who experienced an exacerbation showed a significant decline in fatigue, emotion and mastery domain score of CRQ and symptoms score of SGRQ. A clinically significant decline (more than 4 units) during the six months was observed in SGRQ symptoms score. In patients experiencing two or more exacerbations, all SGRQ sub scores and total SGRQ score declined additionally. Multiple regression analysis indicated that exacerbation frequency independently predicted decline in mastery score of CRQ and symptom score of SGRQ.

Llor et al.¹¹ found that patients who experienced exacerbations during a two-year follow-up period, had a significantly worse evolution of SGRQ total score compared to patients who did not experience exacerbations (+0.2 units vs -5.3 units). Furthermore, patients experiencing two or more exacerbations during follow-up showed an average increase of 2.4 units in SGRQ compared to an average decrease of 3.77 units in patients who experienced one exacerbation.

In line with this, Spencer et al.¹⁸ showed that both infrequent exacerbators (<1.65 exacerbations per year) and frequent exacerbators (> 1.65 exacerbations per year) presented a significant greater increase in SGRQ compared to non-exacerbators during a follow-up period up to three years. However, frequent exacerbator showed a larger worsening in health status than infrequent exacerbators.

Esteban et al.¹³ compared the impact of hospitalization due to an AECOPD on SGRQ and SF-36 scores and found a significant worsening in all domains and total score of SGRQ and in physical functioning scores of SF-36 in patients who had ≥ 3 hospitalizations

during a five years follow-up period. Physical functioning score was also decreased to a less extent in patients who were hospitalized one or two times during follow-up.

Anzueto et al.¹⁵ reported a sub analysis investigating the impact of AECOPD on health status in two randomized controlled trials assessing the effectiveness of tiotropium. Compared to baseline, the largest improvements of SGRQ occurred in patients that did not experience exacerbations during the one-year follow-up period. In the placebo grouper, an association was found between the frequency of exacerbations and worsening of SGRQ scores.

Steele et al.¹⁴ reported no significant difference in the impact of PR on SOLDQ, SF-36 and Walking self-efficacy between rehab completers who did or did not experience an exacerbation throughout the rehabilitation period.

Table 3. Influence of (repeated) exacerbations on changes in health status over time in patients with COPD						
Author(s), year	Study design/ Time of assessment	Sample size	Patient characteristics baseline	Functional capacity assessment instrument	How to diagnosed an exacerbation	Main results
Anzueto, Leimer & Kesten, 2009	Retrospective post-hoc analyses of two previously reports 1-y placebo-controlled clinical trials Baseline and every 6 months during 1 year	Two groups according to the treatment received: Tiotropium: n=550 Male: n=366 Female: n=184 Placebo: n=371 Male: n=233 Female: n= 138	Tiotropium Age, y= 65±9 FEV ₁ ,%= 39.1±13.7 BMI, kg/m ² = NA Placebo Age, y= 65±9 FEV ₁ ,%= 38.1±14.1 BMI, kg/m ² = NA	FEV ₁ SGRQ Baseline Dyspnea Index (BDI) Transition Dyspnea Index (TDI)	Defined as a complex of respiratory events (i.e., cough, wheezing, dyspnea or sputum production) lasting >3days, generally treated with antibiotics and/or oral steroids and report by the investigator as an adverse event	<i>Divided patient in accordance with the number of exacerbations during the 1-y follow up: 0, 1, 2 and >2</i> Values described as a change from baseline SGRQ , mean (SE) Tiotropium: 0 (n=326): ↓ 4 (0.7) 1 (n=111): ↓ 2.7 (1.1) 2 (n=44): ↓ 1.3 (1.8) >2 (n=35): ↓ 3.4 (2.0) Placebo: 0 (n=175): ↓ 1.5 (0.9)* 1 (n=92): ↑ 0.9 (1.2)* 2 (n=34): ↑ 2.6 (2.0) 3 (n=23): ↑ 5.3 (2.5)* *p<0.05 tiotropium vs placebo Number of exacerbation per year according to the end-of-treatment scores Tiotropium: TDI focal score ≤-1: 1.4

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						<p>TDI focal score 0: 0.69 TDI focal score \geq-1: 0.62</p> <p>Placebo: TDI focal score \leq-1: 1.50 TDI focal score 0: 0.87 TDI focal score \geq-1: 0.62</p> <p>Tiotropium: SGRQ total score \geq-4: 0.85 SGRQ total score \geq0, <4: 0.76 SRQ total score >-4, <0: 0.80 SGRQ total score \leq-4 -1: 0.69</p> <p>Placebo: SGRQ total score \geq-4: 1.14 SGRQ total score \geq0, <4: 0.87 SRQ total score >-4, <0: 1.09 SGRQ total score \leq-4 -1: 0.67</p>
Cote et al., 2007	<p>Observational prospective study</p> <p>Baseline</p> <p>Acute: immediately after exacerbation</p> <p>6-months, 1 and 2-years after exacerbation</p>	<p>Non exacerbator: n= 75 Male: n=72 Female: n=3</p> <p>COPD exacerbators patients: n= 130 Male: n=122 Female: n= 8</p>	<p>- Non exacerbator Age, y= 67\pm9 FEV₁,%=48.5\pm16 BMI, kg/m²= 28\pm6.27</p> <p>- Single exacerbators: Age, y= 65\pm9</p>	6MWT BODE index	<p>Defined as an event characterizes by a sustained worsening of respiratory symptoms for at least 2 days, requiring the following: a visit to a doctor or the</p>	<p>Changes during the exacerbation and after the initial episode compared to baseline</p> <p>- Non exacerbators: 6MWD 1-y after: \uparrow 17m (4.7%) 2-y after: \uparrow 1 m (0.28%) p= NS</p>

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		<p>Divided in:</p> <p>Single exacerbators: n=48</p> <p>Male: n=46 Female: n=2</p> <p>Frequent exacerbators: n= 82</p> <p>Male: n=76 Female: n=6</p>	<p>FEV₁,% =42.6±15.54</p> <p>BMI, kg/m²= 27.39±6.17</p> <p>- Frequent exacerbators: Age, y= 68±9</p> <p>FEV₁,% =37.68±14.3</p> <p>BMI, kg/m²= 27.42±5.84</p>		<p>emergency department; and treatment with antibiotics or systemic steroids or both, but no necessitating a hospitalization</p>	<p>BODE</p> <p>6-mo after: ↓ 0.22pt (6%) 1-y after: ↓ 0.17pt (4.7%) 2-y after: ↓ 0.07pt (1.9%) p= NS</p> <p>Change from baseline</p> <p>- COPD exacerbators patients:</p> <p>6MWD</p> <p>6-mo after: ↓ 37m (10.5%) 1-y after: ↓ 49m (13.9%) 2-y after: ↓ 72m (21%) p=0.0004 (intragroup comparison)</p> <p>BODE</p> <p>6-mo after: ↑ 0.71pt (16.7%) 1-y after: ↑ 0.8pt (18.8%) 2-y after: ↑ 1.09pt (25.6%) p=0.001 (intragroup comparison)</p> <p>- Single exacerbators:</p> <p>6MWD</p> <p>1-y after: ↓ 51m (13%), p=0.03 2-y after: ↓ 81m (21%), p= 0.01</p> <p>mMRC</p> <p>-y after: ↑ 0.23pt (10), NS 2-y after: ↑ 0.17pt (7.9%), NS</p> <p>BODE</p>
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						<p>1-y after: ↑ 0.7pt (20%) , p=NS 2-y after: ↑ 0.81pt (21.8%), p=NS</p> <p>- Frequent exacerbators:</p> <p>6MWD 1-y after: ↓ 49m (15%), p=0.01 2-y after: ↓ 67m (20%), p= 0.002</p> <p>mMRC 1-y after: ↑ 0.26pt (11%), p=0.05 2-y after: ↑ 0.38pt (716%), p=0.009</p> <p>BODE 1-y after: ↑ 0.89pt (19%) , p=0.004 2-y after: ↑ 1.14pt (25%), p=0.0005</p> <p>Values of SD not provided</p>
Dreyse et a., 2015	<p>Observational prospectively study</p> <p>- Baseline - Every 6 months until 2 years follow-up</p>	<p>n= 100 COPD patients male: n=58 female: n=42</p> <p>Divided in: Infrequent exacerbators (<2 exacerbation/year): n=51 Male: n= 31 Female: n=20</p>	<p>Age, y= 68.8±7.7 FEV₁,%= 52.6±20 BMI, kg/m²= 26.6±3.7</p> <p>Infrequent exacerbators Age, y= 68.8±6.5 FEV₁,%= 57.6±19.3 BMI, kg/m²= 26.7±3.5</p>	<p>6MWT SGRQ CRQ mMRC</p>	<p>A sustained worsening of the patient's condition from the stable and beyond normal day-to-day variation that is acute onset and necessitates a change in regular medication</p>	<p>6MWD and CRQ are lower in frequent exacerbators without differences across time</p> <p>SGRQ and mMRC are higher in frequent exacerbators without differences across time</p>

		Frequent exacerbators (≥ 2 exacerbation/year): n=49 Male=27 Female=22	Frequent exacerbators Age, y= 68.8 \pm 8.8 FEV ₁ ,%= 47.6 \pm 20.8 BMI, kg/m ² = 26.5 \pm 4			
Esteban et al., 2009	Observational prospectively study Baseline 5 years after the initial assessment	n=391 patients Divided concerning the amount of hospitalization in the 5-y follow up period: -not hospitalized: n=287 Male: NA Female: NA -1-2 times: n= 76 Male: NA Female: NA - ≥ 3 times: n= 28 Male: NA Female: NA	-not hospitalized: Age, y= 65.2 \pm 8.8 FEV ₁ ,%=53.9 \pm 13.7 BMI, kg/m ² = 27.8 \pm 4.0 -1-2 times: Age, y= 66.6 \pm 8.87.4 FEV ₁ ,%=49.5 \pm 13.7 BMI, kg/m ² = 28.6 \pm 5.4 - ≥ 3 times: Age, y= 64.9 \pm 8.8 FEV ₁ ,%= 44.6 \pm 13.3 BMI, kg/m ² = 28.6 \pm 4.6	SGRQ SF-36: - Mental component summary (MCSS) - Physical component summary (PCSS)	Information on hospital admission due to COPD exacerbation was obtained by analyzing the database for the hospital, which is the benchmark hospital for the patients enrolled in the study.	-not hospitalized: Baseline – 5-y follow-up, p-value: change from baseline SGRQ - symptoms: 37.9 \pm 20.8 – 39.0 \pm 22.1, p=NS - activity: 47.6 \pm 20.4 – 44.0 \pm 24.1, p<0.05 - impact: 37.9 \pm 20.8 – 28.6 \pm 20.9, p=NS - total: 36.0 \pm 17.7 – 35.0 \pm 19.9, p=NS SF-36 - MCSS: 49.9 \pm 11.3 – 51.5 \pm 11.3, p<0.05 - PCSS: 46.2 \pm 8.0 – 41.1 \pm 8.7, p<0.05 - 1-2 times Baseline – 5-y follow-up SGRQ - symptoms: 46.7 \pm 21.3 – 50.3 \pm 21.0, p=NS - activity: 57.2 \pm 22.9 – 55.4 \pm 25.3, p=NS - impact: 34.0 \pm 19.7 – 37.8 \pm 21.3, p=NS - total: 43.1 \pm 18.9 – 45.2 \pm 19.5, p=NS

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					<p>SF-36</p> <ul style="list-style-type: none"> - MCSS: 4=50.3±10.6 – 50.9±11.5, p=NS - PCSS:44.2±7.9 – 37.4±8.9, p<0.05 <p>- ≥ 3 times: Baseline – 5y follow-up</p> <p>SGRQ</p> <ul style="list-style-type: none"> - symptoms: 47.0±18.0 – 61.8±19.2, p<0.05 - activity: 58.1±20.5 – 69.1±21.9, p<0.05 - impact: 34.8±17.7 – 49.6±22.4, p<0.05 - total: 43.9±16.4 – 57.5±19.5, p<0.05 <p>SF-36</p> <ul style="list-style-type: none"> - MCSS: 49.7±10 – 45.6±13.3, p<0.05 - PCSS:45.2±6.0 – 34.7±7.8, p=NS <p>Also divided the patients with FEV1≥50% at baseline:</p> <ul style="list-style-type: none"> - clinically significant difference in SGRQ total between patients who were not hospitalized over the study period and those who were - after 5-y follow-up clinically and statistically significant declines were observed in all areas of the SGRQ as well as PCSS and MCSS among patients who were hospitalized during the study period and those who were not.
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<p>Ferrari et al., 2011</p>	<p>Observational longitudinal study</p> <p>Baseline and after 3 years</p>	<p>n= 95 Male: n= 63 Female: n= 32</p>	<p>Age, y= 64±9 FEV₁,%= 59.3±23.2 BMI, kg/m²= 25.9±5.8</p>	<p>SGRQ 6MWT BODE index</p>	<p>Defined as an increase in dyspnea, sputum purulence, and increase sputum volume and classified as moderate (requiring visit to a doctor or the emergency department and treatment with antibiotics or systemic steroids or both) or severe type II (requiring hospital admission)</p>	<p>72 (75.8%) patients had at least one exacerbation during the study and in these patients the baseline SGRQ total score was significantly higher [44(30-61(%))] in those without exacerbation [27(14-39)%], p<0.001]</p> <p>Baseline – After 3 years, all patients.</p> <p>SGRQ</p> <ul style="list-style-type: none"> - activity: 52±21 – 60±22, p<0.001 - total: 42±19 - 44±19, p=0.041 <p>6MWM, baseline – after 3 years, all patients</p> <p>6MWD: 437.7±85.6m – 412.4±100m, p=0.001</p> <p><i>Multiple linear regression:</i></p> <p>BODE was selected as predictor of SGRQ total score (r²= 0.46, p<0.001) and after three years, both BODE index and patient age were predictors in the model with (r²= 0.49, p<0.001) and without exacerbation (r²= 0.51, p<0.001).</p> <p>When BODE index was replaced by its variables (BMI, MMRC, FEV₁ and 6MWD) and number of exacerbations as included in the model, the predictors of health status were MMRC, FEV₁ and exacerbation (r²= 0.63, p<0.001).</p>
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<p>Hopkinson et al., 2007</p>	<p>Observational prospective study</p> <p>Baseline and 1 year follow-up</p>	<p>COPD patients: n= 64</p>	<p>Age, y= 62±9.4 FEV₁,%=36±18.4 BMI, kg/m²= 24.3±5.2</p>	<p>SGRQ Fat free mas (FFM) Maximum isometric quadriceps strength (QMVC)</p>	<p>Change in the patient's baseline dyspnea, cough and/or sputum beyond day-to-day variability sufficient to warrant a change in management</p>	<p>36 (56%) of the patients were defined as frequent exacerbators.</p> <p>Values described as pre – one-year follow-up, p-value for all patients.</p> <p>- QMVC(kg)= 34.8±1.5 – 33.3±1.5, p<0.05 - QMVC (%pred)= 66.3±17.9 – 62.3±17.7, p<0.05</p> <p>Decline in QMVC was not associated with disease severity, having frequent exacerbations or corticosteroid treatment.</p> <p>- FFM (kg)= 47.5±8.3 – 47.3±7.9 Having frequent exacerbation associated with decline in FFM (r= - 0.34, p=0.006)</p>
<p>Kardos et al., 2017</p>	<p>Observational prospectively study</p> <p>- Baseline - 1 year follow-up - 2 years follow-up</p>	<p>n= 3137 COPD patients</p> <p>Male: n= 1854 (59.1%) patients Female: n= 1283 (40.9%) patients</p>	<p>Age, y= 65.6 ± 10.1 FEV₁,%=62.9 ± 24.4 BMI, kg/m²= 27.3±5.6</p>	<p>COPD Assessment Test (CAT)</p>	<p>Defined by prescription of oral steroids and/or antibiotics or hospitalization</p>	<p>CAT, change from baseline After 1-y= ↓ 1.8 ± 5.8 After 2-y= ↓ 2.3 ± 6.5</p> <p><i>Assessed the proportion of patients with a clinically relevant improvement (≥2 units) or worsening from baseline:</i></p> <p>- Improvement, number (%) of patients: After 1-y= 1554 (49.5%) patients After 2-y= 1701 (54.2%) patients</p>

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					<p>- Worsening, number (%) of patients: After 1-y= 918(29.3%) patients After 2-y= 710 (22.6%) patients</p> <p>Exacerbation rate was lower in patients with a sustained improvement (0.324 [95% CI 0.284, 0.370] over the 2-y follow up) than those with a sustained worsening (0.529 [0.440, 0.636])</p> <p><i>Percentage of patients in GOLD ABCD:</i></p> <p>GOLD A Baseline: 6.2% After 1-y= 9.0 % After 2-y= 10.5 %</p> <p>GOLD B Baseline: 45.9% After 1-y= 56.1 % After 2-y= 53.6 %</p> <p>GOLD C Baseline: 3.1% After 1-y= 2.9 % After 2-y= 2.7 %</p> <p>GOLD D Baseline: 44.7% After 1-y= 31.5 % After 2-y= 32.7 %</p>
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Llor et al., 2008	Observational prospective study Baseline and every 6 months during 2 years	n= 136 COPD patients divided in two groups: -Without exacerbation: n=46 Male: n= 44 Female: n=2 - With exacerbation: n= 90 Male: n= 87 Female: n= 3	- Without exacerbation: Age, y= 68.9±9.7 FEV ₁ ,%=47.7±14.6 BMI, kg/m ² = NA - With exacerbation: Age, y= 70.2±9.5 FEV ₁ ,% =50.7±14.4 BMI, kg/m ² = NA	SGRQ	Defined by the symptoms: an increase in dyspnea, expectoration and/or in the purulence of the sputum	COPD patients with exacerbation (n=90): - SGRQ score : ↑ 0.2 (IC95% NA), p<0.789 <i>Subdivided patients in two groups:</i> - With one exacerbation (n=32) SGRQ score: ↓ 3.77 (IC95% (-2.1) – (-5.1)), p<0.023 - With two or more exacerbations (n=58) SGRQ score: ↑ 2.4 (IC95% 1 – 4.1), p<0.13
Nishimura et al., 2009	Observational longitudinal study Baseline and every 6 months - If presents an exacerbation: 6-week exacerbation-free period	156 COPD patients divided in two groups: -Without exacerbation: n=108 Male: n= 103 Female= 5 - With exacerbation: n= 48 Male: n= 46 Female: n= 2	- Without exacerbation: Age, y= 71.4±6 FEV ₁ ,%=49.3±15.4 BMI, kg/m ² = NA - With exacerbation: Age, y= 71.4±7 FEV ₁ ,% =40.7±10.9 BMI, kg/m ² = NA	SGRQ CRQ	Defined as a worsening if respiratory symptoms that required treatment with oral corticosteroids or antibiotics or both	Values described as a change from baseline COPD patients with exacerbation (n=48): - CRQ (mean±SE) Fatigue domain: ↓ 0.35±0.15 question, p<0.05 Emotion domain: ↓ 0.3±0.12 question, p<0.05 Mastery domain: ↓ 0.4±0.15 question, p<0.05 Total Score: ↓ 0.3±1/ question, p<0.05 - SGRQ

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					<p>Symptoms score: $\uparrow 5 \pm 2$ pt, $p < 0.05$ Activity: 1.75 ± 1 pt, $p = \text{NS}$ Impact: 0.5 ± 1 pt, $p = \text{NS}$ Total: 1.75 ± 1.25, $p = \text{NS}$</p> <p><i>Performed additional analyses on those subjects with frequent exacerbations (n=12)</i></p> <p>- CRQ Fatigue domain: $\downarrow 0.54 \pm 0.22$ question, $p < 0.05$ Emotion domain: $\downarrow 0.54 \pm 0.32$ question, $p < 0.05$ Mastery domain: $\downarrow 0.6 \pm 0.3$ question, $p < 0.05$</p> <p>- SGRQ Symptoms score: $\uparrow 12.4 \pm 5.6$ pt, $p < 0.05$ Activity score: $\uparrow 5.1 \pm 2.4$ pt, $p < 0.05$ Impact score: $\uparrow 4.4 \pm 2.1$ pt, $p < 0.05$ Total: $\uparrow 6.1 \pm 2$ pt, $p < 0.05$</p> <p>Regression - increase in the occurrence of an acute exacerbation caused a significant deterioration in the health status in: - CRQ fatigue (odds ratio (OR) = 1.77, $p = 0.02$); - CRQ mastery (OR=1.92, $p = 0.01$); - SGRQ symptoms (OR=0.97, $p = 0.001$)</p>
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<p>Rubinsztajn et al., 2016</p>	<p>Observational prospectively study</p> <p>- Baseline -After 12-months - After 24-months</p>	<p>Baseline n= 445 COPD patients</p> <p>After 24-months: n= 261 COPD patients</p> <p>Divided patients in: 0-1 exacerbation/year: n=190</p> <p>≥2 exacerbation/year: n= 71</p>	<p>Age, y= 66.4±9.2 FEV₁, %= 50.2±15.8 BMI, kg/m²= 26.6±5.6</p> <p>0-1 exacerbation/year: Age, y= NA FEV₁, %= 53.1±18.5 BMI, kg/m²= NA</p> <p>≥2 exacerbation/year: Age, y= NA FEV₁, %= 46.3±16.7 BMI, kg/m²= NA</p>	<p>SGRQ mMRC</p>	<p>Self-reported and recorded in a diary</p>	<p>SGRQ and mMRC</p> <p>Non-significant difference thought out the study period</p> <p>0-1 exacerbation/year: SGRQ</p> <p>- symptoms: 49.4±20.4 - activity: 61.7±21.2 - impact: 35.8±18.3 - total: 46.1±18.8</p> <p>≥2 exacerbation/year: SGRQ</p> <p>- symptoms: 61,2±25.2 - activity: 75.9±17.1 - impact: 53.2±17.3 - total: 61.6±14.4</p> <p>Comparing 0-1 exacerbation/year vs ≥2 exacerbation/year: - symptoms; activity; impact and total: p<0.001</p>
<p>Spencer et al., 2004</p>	<p>Randomized, double-blind, placebo-controlled, parallel-group</p> <p>Baseline and every 6 months during 3 years</p>	<p>Categorized patients in: -Non- exacerbators: n=91 Male: n=80 Female: n=11</p> <p>- Infrequent</p>	<p>- Non-exacerbators: Age, y= 65±7 FEV₁,%=55±15 BMI, kg/m²= NA</p> <p>- Infrequent exacerbators:</p>	<p>SGRQ</p>	<p>Defined as “chest problems requiring treatment with antibiotics and/or oral corticosteroids”</p>	<p>SGRQ, decline rate compared with baseline</p> <p>-Non- exacerbators: ↑ 2 (IC 95% 1.7-2.3) units.y⁻¹</p> <p>-Infrequent exacerbator: ↑ 2.4 (IC 95% 2.2-2.6) units.y⁻¹</p>

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		<p>exacerbators: n=285 Male: n=209 Female: n=76</p> <p>- Frequent exacerbators: n=235 Male: n=211 Female: n=24</p>	<p>Age, y= 63±7 FEV₁,%=53±15 BMI, kg/m²= NA</p> <p>- Frequent exacerbators: Age, y= 64±7 FEV₁,%=45±13 BMI, kg/m²= NA</p>			<p>-Frequent exacerbator: ↑ 2.9 (IC 95% 2.6-3.1) units.y⁻¹, p<0.004 vs non-exacerbators and p=0.004 vs infrequent</p>
Steele et al., 2010	<p>Clinical trial</p> <p>Pre and during the final week of the PR program</p>	<p>n=146 patients Male: n= 140 Female: n=6</p> <p>Divided in those who experienced an exacerbation and those who not experienced an exacerbation during the PR:</p> <p>- Non-exacerbators: n=116</p> <p>- Exacerbators: n=30</p>	<p>Non-exacerbators: Age, y= 66±8 FEV₁,%= 39.8±15.8 BMI, kg/m²= 30.8±7.5</p> <p>Exacerbators and completers, n=20: Age, y= 69±9 FEV₁,%= 36.3±14.9 BMI, kg/m²= 28.6±6.3</p> <p>Exacerbators and non-completers: Age, y= 68±6.7 FEV₁,%= 25.3±10.8 BMI, kg/m²= 26.3±2.5</p>	<p>PAL Seattle Obstructive Lung Disease Questionnaire (SOLDQ) 6MWT SF-36 Walking Self-Efficacy Questionnaire</p>	<p>Defined as reported sustained worsening of dyspnea along with cough or sputum production for at least 2 days necessitating an increase in bronchodilator use as well as episodic prednisone or antibiotic.</p>	<p>Values pre – post PR, change from pre PR</p> <p>Exacerbators: Daily activity, VMU: 162.8±89.2 – 166.7±81.3 6MWD, ft: 1053±391 – 1263±370, ↑ 210* 6MWD, m: 320.95±119.17 – 384.96±112.7, ↑ 64</p> <p>Self-efficacy for walking: 2.4±2.3 – 2.8±2.6 SF-36 physical: 33.6±12.9 – 35.8±13.8 SF-36 emotional: 52.2±23 – 65.7±17 SOLDQ physical: 22.6±12.9 – 35.8±13.8 SOLDQ emotional: 522.2±23 – 65.8±17 SOLDQ self-management: 63.1±22.3 – 74.0±19.7</p> <p>Non-exacerbators:</p>

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						<p>Daily activity, VMU: 164.9±142.9 – 142.8±58.8</p> <p>6MWD, ft: 1171±345 – 1334±338, ↑ 163*</p> <p>6MWD, m: 356.92±105.15 – 406.6±103, ↑ 49.6</p> <p>*p=0.04, analysis of covariance of change scores for PR outcomes</p> <p>Self-efficacy for walking: 3.3±2.5 – 3.8±2.7</p> <p>SF-36 physical: 36.9±16.4 – 44.1±18.8</p> <p>SF-36 emotional: 58.9±21.4 – 68.3±21.1</p> <p>SOLDQ physical: 36.9±16.4 – 44.1±18.8</p> <p>SOLDQ emotional: 58.9±21.4 – 69.3±21.1</p> <p>SOLDQ self-management: 69.1±19.6 – 75.1±19.3</p>
<p>Legend: 6MWD= six-minute walking distance; 6MWT= six-minute walking test; BMI= body mass index; BODE= body mass, obstruction, dyspnea and exercise capacity; CRQ= Chronic Respiratory Disease Questionnaire; FEV₁= forced expiratory volume in the first second; mMRC= Medical Research Council scale for dyspnea; NA= not available; NS= non significant; SE= standard error; SF-36= 36-item short form survey; SGRQ= Saint Georges' Respiratory Questionnaire.</p>						

Discussion

This review summarizes the effect of a single and (repeated) exacerbations on changes in health status in patients with COPD. Literature suggests that a single exacerbation has a temporary negative impact on complaints and physical activity levels, regardless of the severity of the exacerbation. Patients who frequently experience exacerbations have a worse quality of life and more complaints. The impact of (repeated) exacerbations on exercise tolerance and muscle function is less clear from the available literature.

Health status is defined as the impact of health on patients' ability to perform and derive fulfilment from the ADL²². Many health status instruments were used for different purposes, including performance-driven and patient-reported measures²³⁻²⁶. Vercoulen et al. (2008)¹ suggested a sub-classification of health status in patients with COPD encompassing different sub-domains of health status which allows a more concrete and detailed definition of health status. As the sub-domains of health status are relatively independent, the integral assessment of health status therefore is essential for tailoring interventions to the needs of each patient¹.

Effect of (repeated) acute exacerbations on health status beyond the lungs

- Physiological impairment

An exacerbation acutely decreases functional exercise tolerance, as assessed with a 6MWD test^{6,16}. This finding is as expected as breathing load is acutely increased and patients experience breathlessness even when performing low intense activities. Interestingly, literature suggests that this decrease is maintained during up to two years of follow-up^{4,16}. The role of exacerbation frequency in this long-term process is unclear based on conflicting results in literature. The lack of additional worsening of 6MWD in patients with a repeat exacerbation during follow-up – as reported by Cote et al.¹⁶ – might indicate that the relevance of the index exacerbation in the long-term decline of functional exercise tolerance should not be minimized. The findings of Dreyse et al.⁴ – who showed that patients experiencing more than 2 exacerbations per year on average had consistently lower 6MWD – however suggests that patients with multiple exacerbations per year are at specific risk of developing exercise intolerance. Such exercise intolerance might be related to a progressive decline in pulmonary function and/or the development or worsening of peripheral muscle impairment.

Findings about changes in peripheral muscle strength due to acute exacerbations are somewhat conflicting^{6,20}. Alahmari et al.⁶ found an immediate decrease of quadriceps strength due to a single exacerbation. This is in line with findings of Spruit et al.²⁷ who reported a 1% decrease in quadriceps strength throughout hospital admission for an acute exacerbation and only a partial recovery 90 days after discharge. In this trial, quadriceps strength during the acute exacerbation was significantly related to blood markers of systemic inflammation and growth hormone levels. It is known that frequent exacerbators elicit high levels of airway and systemic inflammatory markers^{28,29}. Besides systemic inflammation, multiple other factors have the potential to induce muscle impairment during an exacerbation, including oxidative stress which stimulate proteolysis, depress protein synthesis and induces apoptosis³⁰, hypoxia, hypercapnia, use of oral corticosteroids and androgen deprivation.

Therefore, it is surprising that Hopkinson et al.²⁰ found no association between exacerbation frequency and the decline in quadriceps muscle strength over one year, despite an established association with fat free mass. It would be interesting to investigate longitudinal changes in peripheral muscle strength over a longer period of follow-up (e.g. 3 to 5 years), which might allow enhanced identification of changes in muscle strength beyond test variability and better stratification of (in)frequent exacerbators. Still, the currently available evidence did not report about the impact in activities of daily living itself. Therefore, future research may also assess specifically it.

- Complaints

Regarding the complaints, (repeated) exacerbations induce an increase in symptoms during ADL – both dyspnea and fatigue^{4,6}. Dyspnea during COPD exacerbation is predominantly related to the worsening of airflow obstruction which implies in additional work of breathing, dynamic hyperinflation and hypoxemia^{31,32} and the mechanisms of increase in fatigue may follow a similar pathway³³. Exacerbation also has an role in the impact of disease over time – assessed by CAT⁹ – and literature suggest a correlation between the impact of disease and functional status³⁴.

- Functional impairment

Functional impairment can be found after an exacerbation, with reduction in physical activity level^{6,7} and reduction in daily steps count. Repeated exacerbations are, in addition, associated with a faster decline in daily step-count⁵ and in time spent outdoors¹² As reported by Pitta et al.³⁵, COPD patient also remain inactive even one month after discharge,

elucidating that physical inactivity is not simply the result of bed rest during the hospitalization. Physical inactivity leads to the start of a vicious circle of inactivity and deconditioning³⁶, and the peripheral muscle dysfunction²⁷ and decrease in functional capacity are themselves associated with physical inactivity in exacerbated patients.

Besides, dynamic hyperinflation plays a role during exacerbation^{37,38} in the reduction of physical activity acutely, since it reduces the ability of tidal volume to expand appropriately during exercise and this leads to early mechanical limitation of ventilation³⁹, functional inspiratory muscle weakness – by the increases in the elastic and threshold loads on the inspiratory muscles – and increases the breathlessness^{38,40}. However, in long term, it is described that indices of hyperinflation and gas trapping improved after 60 days of an exacerbation episode with a consequent improvement in dyspnea³² it is probably not the underlying causes of physical inactivity on the long term. Besides that, no data on longer term effects in physical activity level were found by the present review.

- *Quality of life*

A long-term effect of an acute exacerbation in health-related quality of life was widely studied. Patients who experienced frequent exacerbations had a greater decline in health-related quality of life over time^{4,10,17,18}. Further, exacerbation rate has a detrimental and cumulative effect on health status^{17,18}, and declines in the quality of life were observed regardless of the initial severity of disease¹³. These findings corroborate the findings of large cohort trials, showing an association between hospitalization(s) for an exacerbation and impairment of health-related quality of life^{41,42}. As we described previously, exacerbation has a great impact in all subdomains of health status – physiological (impairment in functional capacity, muscle dysfunction), complaints (increase symptoms), functional (decrease physical activity) and quality of life – these subdomains were relatively independent, as described by Vercoulen and colleagues, and assessing these subdomains can give a much more concrete and more detailed definition concerning health status.

Implications for care

These findings suggest that at least a subset of patients show a sustained worsening in health status beyond the lungs after experiencing one or repeated exacerbations. These patients might be excellent candidates for a comprehensive multidisciplinary intervention that tackles the patient's health status beyond the lungs, namely pulmonary rehabilitation. Early rehabilitation leads to a reduction in hospital admissions, increase in

exercise tolerance and quality of life health status^{43,44} and it is associated with reduced readmission and shortened length of stay in patients with exacerbation of COPD⁴⁵. Our findings also indicate that physical activity behavior is an important outcome to be addressed in these patients. Therefore, the inclusion of behavioral change interventions seems to be essential to provide optimal results in terms of health status.

Methodological considerations

We performed a thorough systematic screening process by two independent reviewers. Eleven of the included studies were rated as good, five studies were rated as fair and one was rated as poor. Screening criteria were clearly defined a priori and the search strategy was comprehensive in order to identify all relevant studies. However, we only performed this search strategy in PubMed and might have missed articles that are not available in this database⁴⁶. Further, the methodological quality of some studies was not classified as high in six out of 17 studies, which might impact to some extent on the validity of our conclusions.

We acknowledge that several concepts are used to define health status and numerous tools have been designed to assess aspects of health status. For clarity, we systematically worked with a previously published assessment framework for health status in patients with COPD, as proposed by Vercoulen et al.¹. The allocation of health status instruments to one of the proposed sub-domains might be arbitrary to some extent and one instrument might cover aspects of several sub-domains of health status.

Conclusion

The results of this review of 17 studies clearly reveals the detrimental impact of (repeated) exacerbations of COPD on complaints, physiologic and functional impairment as well as quality of life. Although the long-term impact of (repeated) exacerbations on exercise tolerance, muscle strength and physical activity levels is less clear and/or conflicting evidence is existing.

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Chapter 5

Final considerations & implications for care

Summarizing the findings of the three manuscripts presented in this thesis, first of all, a correlation was found between metabolic limitations (increased metabolic demand) and ventilatory limitations (dyspnea and increased ventilatory demand during ADL) with the activity of daily living limitation, assessed by LCADL scale and the quality of life through the SGRQ. The total score of SGRQ reflected 67% of the real limitations during ADL such as increased metabolic demand and dyspnea. And when we applied the LCADL, it can reflect in 34% the real limitations during ADL.

Secondly, an equivalent improvement in ADL dyspnea and LCADL following by improvements in exercise capacity and muscle strength after both LL/HR and HL/LR was noticed with a superior effect of LL/HR training in symptoms domain of SGRQ.

It becomes important to give attention to the scores in both LCADL and SGRQ, since it reflects limitation during real-life situation, furthermore it is known that patients usually present limitation at the very early stage of efforts. We also recommend that some energy conservation techniques (ECT) should be taught to these patients, avoiding them to lose function in basic ADL. The more ability to perform ADL the lower the symptoms and limitations and the more physically active the patient will be.

Concerning the exercise training, both low and high load resistance training could be used, and the specificity of the training protocol should be take into account, thinking in the outcomes that patient should improve to have great performance in your daily living, which will be reflected in the improvement of quality of live. The inclusion of exercises with more functional characteristics, in which the goal is to improve the performance in ADL, should be consider in pulmonary rehabilitation programs.

Both SGRQ and LCADL, which are widely used are feasible to represent real limitations of the patients. In this way, it is possible to assess these patients with focus in ADL limitation and, afterwards, teach the patient how to improve the execution of this activities and also add in pulmonary rehabilitation functional exercises.

And finally, regarding to exacerbation, it was clearly revealed the detrimental impact of (repeated) exacerbations of COPD on complaints, physiologic and functional impairment as well as quality of life. Although the long-term impact of (repeated) exacerbations on exercise tolerance, muscle strength and physical activity levels is less clear and/or conflicting evidence is existing.

These findings suggest that at least a subset of patients show a sustained worsening in health status beyond the lungs after experiencing one or repeated exacerbations. These patients might be excellent candidates for a pulmonary rehabilitation. Our findings also indicate that physical activity behavior is an important outcome to be addressed in these patients. Therefore, the inclusion of behavioral change interventions seems to be essential to provide optimal results in terms of health status.

Appendices

Appendix A. Informed consent

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

Você está sendo convidado(a) para participar da pesquisa **“IMPACTO DO TREINAMENTO AERÓBIO E TREINAMENTO RESISTIDO EM DIFERENTES INTENSIDADES NO DESEMPENHO EM ATIVIDADES DE VIDA DIÁRIA E ÍNDICE BODE EM PACIENTES COM DPOC.”**

Você foi selecionado para participar porque apresenta diagnóstico clínico de doença pulmonar obstrutiva crônica (DPOC) moderada a grave, constatado pela espirometria; está estável, sem história de infecções, aumento dos sintomas respiratórios ou mudança de medicamentos nos dois meses anteriores ao estudo; faz uso ou não de oxigênio; não fumante ou ex-fumante e apresenta pontuação da versão modificada do questionário Medical Research Council modificado (mMRC) maior ou igual a 2. Além disso, você foi encaminhado pelo médico para à Unidade de fisioterapia respiratória na Unidade Saúde Escola (USE) ou na Unidade Especial de Fisioterapia Respiratória da UFSCar, porém sua participação não é obrigatória.

Os objetivos deste estudo são verificar quanto o treinamento na bicicleta ergométrica e de dois tipos de treinamento de força influenciam no desempenho e na falta de ar nas atividades do dia-a-dia e nos fatores associados ao aumento da mortalidade dos pacientes com DPOC.

Sua participação nesta pesquisa consistirá em realizar avaliações, programa de reabilitação pulmonar e reavaliações. As avaliações e reavaliações serão compostas por: exame físico, aplicação de escalas e questionários sobre a falta de ar, teste de força dos braços e das pernas, testes de mobilidade e equilíbrio, Teste de Caminhada de 6 minutos (quantos metros caminha durante seis minutos), circuito de atividades do dia-a-dia em laboratório adaptado, Teste de 1 Repetição máxima (qual maior carga que consegue realizar um exercício de força) e Teste de Exercício Cardiorpulmonar Incremental (na bicicleta ergométrica, qual é a carga mais alta que consegue pedalar) e de Carga Constante (quanto tempo consegue pedalar em uma carga pré-determinada).

O programa de reabilitação pulmonar será com treinamento na bicicleta ergométrica, treinamento de força, alongamentos gerais e exercícios de equilíbrio, de 2 a 3 vezes por semana, aproximadamente 1 hora por sessão, totalizando 36 sessões. O protocolo proposto nesse projeto terá todas as atividades que são realizadas normalmente na reabilitação pulmonar, entretanto haverá uma padronização das intensidades e dos exercícios, todos considerados seguros para os pacientes com DPOC. A intensidade do treinamento na bicicleta ergométrica será igual para todos os pacientes, com duração de 20 a 30 minutos. Entretanto, o treinamento de força terá dois grupos de pacientes, que serão divididos por sorteio, que irão fazer o treinamento em duas intensidades diferentes. Os exercícios de força serão em aparelhos de musculação, com dois tipos de exercícios para os braços e um(1) tipo de exercício para as pernas.

Ao participar dessa pesquisa, você receberá acompanhamento e monitorização durante todo tempo, com critérios de segurança. Nos atendimentos, os terapeutas irão perguntar antes, durante e depois do treinamento físico se você apresenta possíveis sintomas (falta de ar, cansaço nas pernas e nos braços, palpitações e batida no peito) e farão monitorização todo o tempo da frequência cardíaca, saturação periférica de oxigênio e medida da pressão arterial. Se ocorrer qualquer sinal e sintoma mínimo anormal, o exercício será interrompido, seguindo os seguintes critérios: aumento da Frequência Cardíaca (FC) acima de 85% da FC máxima prevista para a idade, ou queda de mais de 20% da FC; Pressão Arterial Sistólica maior que 180 mmHg; redução de mais de 20% da Pressão Arterial Sistólica ou Diastólica; Saturação periférica de Oxigênio abaixo de 85%, com ou sem o uso de oxigênio suplementar. Se você estiver com a SpO2 menor do que 88% em repouso ou no exercício, será colocado oxigênio suplementar, e se aumentar a dispneia e “chiado” no peito, o exercício será interrompido imediatamente.

Ao participar desse trabalho, você estará contribuindo para proporcionar maiores esclarecimentos sobre os benefícios do exercício físico em pacientes com DPOC. Terá como benefícios informações sobre alguns aspectos de saúde, dentre eles capacidade funcional, grau de falta de ar, força muscular em pernas e braços, mobilidade e equilíbrio, desempenho nas atividades do dia-a-dia, que tem efeitos sobre a qualidade de vida. Além disso, terá a possibilidade de aproveitar os benefícios a curto prazo do exercício físico e manter sua capacidade física por meio dos exercícios propostos.

Entretanto, você estará sujeito a aumento momentâneo da frequência cardíaca e respiratória, da falta de ar e do cansaço nas pernas resultantes da prática de exercícios físicos, além de dores músculo-esqueléticas e quedas, mas estes riscos serão minimizado ao ser monitorado constantemente pelos pesquisadores.

A qualquer momento você pode desistir de participar e retirar seu consentimento, mediante aviso prévio. Sua recusa não trará nenhum prejuízo em sua relação com o pesquisador ou com o atendimento recebido nas unidades de Fisioterapia Respiratória da UFSCar.

As informações obtidas durante todo o tratamento, bem como imagens (Fotos, Filmagens) da sua participação na avaliação e tratamento serão mantidas em sigilo e não poderão ser consultadas por pessoas leigas, sem a sua autorização. As informações e imagens assim obtidas, no entanto, poderão ser usadas para fins de pesquisa científica, com sua privacidade preservada, utilizando somente as iniciais no nome para identificar os dados relativos a você (exemplo José da Silva – J. S.) e ocultando sua face nas imagens.

Não existe nenhum tipo de seguro de saúde ou de vida, bem como qualquer outra compensação financeira que possa lhe beneficiar em função da participação neste estudo. Não existirão despesas pessoais relativas ao tratamento que será realizado; se houver necessidade de ressarcimento de gastos, será feito pelo pesquisador responsável.

Você receberá uma cópia deste termo onde consta o telefone e o endereço do pesquisador principal, podendo tirar suas dúvidas sobre o projeto e sua participação, agora ou a qualquer momento.

Para questões relacionadas a este estudo, contate:

Ft. Júlia Gianjoppe dos Santos:

Fone: (16) 3376-0198; (16) 98204-7640; e-mail: julia_gian@hotmail.com

Ft. Marina Sallum Barusso

Fone: (16) 997798224; email: mabarusso@gmail.com

Prof^ª. Dr^ª. Valéria Amorim Pires Di Lorenzo:

Fone: (16) 3371-3444; (16) 3351-8343; e-mail: vallorenzo@ufscar.br

Ft. Marina Sallum Barusso

Profa. Dra. Valéria Amorim Pires Di Lorenzo

O pesquisador me informou que o projeto foi aprovado pelo Comitê de Ética em Pesquisa em Seres Humanos da UFSCar que funciona na Pró-Reitoria de Pós-Graduação e Pesquisa da Universidade Federal de São Carlos, localizada na Rodovia Washington Luiz, Km. 235 - Caixa Postal 676 - CEP 13.565-905 - São Carlos - SP – Brasil. Fone (16) 3351-8110. Endereço eletrônico: cephumanos@ufscar.br

Portanto, Eu _____ declaro que entendi os objetivos, riscos e benefícios de minha participação na pesquisa e concordo em participar.

São Carlos,de.....de 20.....

Assinatura do Voluntário

Attachments

Attachment A – LCADL scale

London Chest Activity of Daily Living

Patient ID:

Date of Birth:

Date:

Do you live alone? [] Yes [] No

Self-care

1. Drying []
2. Dressing upper body []
3. Putting shoes/socks on []
4. Washing hair []

Domestic

5. Make beds []
6. Change sheet []
7. Wash windows/curtains []
8. Clean/dusting []
9. Wash up []
10. Vacuuming/sweeping []

Physical

11. Walking upstairs []
12. Bending []

Leisure

13. Walking in home []
14. Going out socially []
15. Talking []

16. How much does your breathing affect you in your normal activities of daily living?

[] A lot [] A little [] Not at all

Score

0. Wouldn't do any way
1. Do not get breathless
2. I get moderately breathless
3. I get very breathless
4. I can't do this anymore because of breathlessness and I have no one else to do it for me
5. I can't do this anymore because of breathlessness and I have someone else to do this for me.

Attachment B – Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies



Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the research question or objective in this paper clearly stated?			
2. Was the study population clearly specified and defined?			
3. Was the participation rate of eligible persons at least 50%?			
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?			
5. Was a sample size justification, power description, or variance and effect estimates provided?			
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?			
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?			
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?			
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			
10. Was the exposure(s) assessed more than once over time?			
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			
12. Were the outcome assessors blinded to the exposure status of participants?			
13. Was loss to follow-up after baseline 20% or less?			
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?			
Quality Rating (Good, Fair, or Poor) (see guidance)			
Rater #1 initials:			
Rater #2 initials:			
Additional Comments (If POOR, please state why):			

Attachment C - Ethics Committee approval



UNIVERSIDADE FEDERAL DE SÃO CARLOS
COMITÊ DE ÉTICA EM PESQUISA EM SERES HUMANOS
Via Washington Luiz, Km. 235 - Caixa Postal 676
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cephumanos@power.ufscar.br <http://www.propq.ufscar.br>

Parecer Nº. 001/2013

Título do projeto: IMPACTO DO TREINAMENTO AERÓBIO E TREINAMENTO RESISTIDO EM DIFERENTES INTENSIDADES NO DESEMPENHO EM ATIVIDADES DE VIDA DIÁRIA E ÍNDICE BODE EM PACIENTES COM DPOC

Pesquisador Responsável: JULIA GIANJOPPE DOS SANTOS

Orientador: VALERIA AMORIM PIRES DI LORENZO

Colaborador(es): MAURICIO JAMAMI; SAMANTHA MARIA NYSSSEN

CAAE: 0354.0.135.000-11

Processo número: 23112.004239/2011-04

Grupo: III

Área de conhecimento: 4.00 - Ciências da Saúde / 4.08 - Fisioterapia e Terapia Ocupacional

Parecer

O projeto foi aprovado pelo parecer 243/2012, sendo a finalidade acadêmica o mestrado da pesquisadora. Devido a um problema de cronograma, e que o projeto ficou por muito tempo em análise, a pesquisadora não a desenvolveu. Já tendo a pesquisa supracitada aprovada, solicitou a este CEP que analisasse uma alteração na finalidade acadêmica do projeto, de mestrado para doutorado, com a devida alteração do cronograma. Por não haver alterações no método de pesquisa e estando o cronograma exequível, considero que não há objeção e declaro o pedido de alteração **aprovado**.

Normas a serem seguidas

- O sujeito da pesquisa tem a liberdade de recusar-se a participar ou de retirar seu consentimento em qualquer fase da pesquisa, sem penalização alguma e sem prejuízo ao seu cuidado (Res. CNS 196/96 – Item IV.1.f) e deve receber uma cópia do Termo de Consentimento Livre e Esclarecido, na íntegra, por ele assinado (Item IV.2.d).
 - O pesquisador deve desenvolver a pesquisa conforme delineada no protocolo aprovado e descontinuar o estudo somente após análise das razões da descontinuidade pelo CEP que o aprovou (Res. CNS Item III.3.z), aguardando seu parecer, exceto quando perceber risco ou dano não previsto ao sujeito participante ou quando constatar a superioridade de regime oferecido a um dos grupos da pesquisa (Item V.3) que requeiram ação imediata.
 - O CEP deve ser informado de todos os efeitos adversos ou fatos relevantes que alterem o curso normal do estudo (Res. CNS Item V.4). É papel do pesquisador assegurar medidas imediatas adequadas frente a evento adverso grave ocorrido (mesmo que tenha sido em outro centro) e enviar notificação ao CEP e à Agência Nacional de Vigilância Sanitária – ANVISA – junto com seu posicionamento.
 - Eventuais modificações ou emendas ao protocolo devem ser apresentadas ao CEP de forma clara e sucinta, identificando a parte do protocolo a ser modificada e suas justificativas. Em caso de projetos do Grupo I ou II apresentados anteriormente à ANVISA, o pesquisador ou patrocinador deve enviá-las também à mesma, junto com o parecer aprobatório do CEP, para serem juntadas ao protocolo inicial (Res. 251/97, item III.2.e).
 - Relatórios parciais e final devem ser apresentados ao CEP, inicialmente dentro de 1 (um) ano a partir desta data e ao término do estudo.
- São Carlos, 26 de fevereiro de 2013.

Profa. Dra. Maria Isabel Ruiz Beretta
Coordenadora do CEP/UFSCar

Attachment D - Manuscript submission

Journal of Cardiopulmonary Rehabilitation and Prevention
Do London Chest Activity Daily Living Scale and Saint George's Respiratory
Questionnaire reflect real limitations during activities of daily living in patients with
COPD?
 –Manuscript Draft–

Manuscript Number:	JCRP-D-17-00078R1
Full Title:	Do London Chest Activity Daily Living Scale and Saint George's Respiratory Questionnaire reflect real limitations during activities of daily living in patients with COPD?
Short Title:	Do LCADL and SGRQ reflect limitation during activities of daily living in COPD patients?
Article Type:	Original Investigation/Manuscript
Keywords:	Activities of Daily Living; quality of life; Functional Limitation; COPD
Corresponding Author:	Valéria Amorim Pires Di Lorenzo, Ph.D. Universidade Federal de Sao Carlos São Carlos, São Paulo BRAZIL
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Order of Authors Secondary Information:	
Manuscript Region of Origin:	BRAZIL
Abstract:	<p>Purpose: It is unclear if activities of daily living (ADL) and quality of life scales reflect the real ADL limitations. The aim of the study was to assess the limitation during ADL simulation and to identify whether the London Chest Activity of Daily Living Scale (LCADL) and Saint George Respiratory Questionnaire (SGRQ) are able to reflect the patient's real limitations during ADL simulation.</p> <p>Methods: Forty-eight COPD patients (69±8yrs; FEV1:1.37±0.49) were assessed by SGRQ and LCADL. An ADL simulation were performed: showering (ADL1), lifting and lowering containers above the shoulder girdle (ADL2), and raising and lowering pots below the pelvic girdle (ADL3).</p> <p>Results: SpO2 and ΔSpO2 in ADL2 were statistically lower compared to ADL3. Ventilatory demand was statistically higher in ADL2 and ADL3 compared to ADL1. MET values were similar between the ADLs with values above 3.6. Oxygen desaturation was present in 33%(ADL1) and 41%(ADL2) of the patients. The LCADL% showed a moderate positive correlation with dyspnea in ADL3 and metabolic demand in ADL1. The SGRQ score presented a moderate positive correlation with dyspnea in all ADL and metabolic demand in ADL1 and ADL3. The dyspnea in ADL3 and metabolic demand in ADL1 explained 33% of the variability in LCADL%. The dyspnea and metabolic demand in ADL3 explained 67% of the variability in SGRQ.</p> <p>Conclusion: ADL lead to oxygen desaturation and high ventilatory demand. LCADL reflects 33% and SGRQ reflects 67% of the functional limitation during ADL simulation, such as dyspnea and the metabolic demand during ADL.</p>

Attachment E - Manuscript submission

Clinical Rehabilitation

Impact of different intensities of resistance training on health status focusing on activities of daily living in patients with COPD: a randomized controlled parallel study

Journal:	<i>Clinical Rehabilitation</i>
Manuscript ID	CRE-2018-6923
Manuscript Type:	Rehabilitation In Practice
Keywords:	Activities of Daily Living, Chronic Obstructive Pulmonary Disease (COPD), Health status, strength training, Pulmonary rehabilitation
Abstract:	<p>Aim: This study sought to determine if two different resistance training intensities improve ADL performance, dyspnea, and quality of life, following by improvement in exercise capacity and muscle strength as well as verify if there is a superiority effect of either of these resistance training intensities. Methods: 24 patients with mild-to-severe COPD (VEF1: $49.7 \pm 14.76\%$; age: 68.8 ± 7.8 years) underwent to 36 sessions of aerobic training combined with resistance training, with difference in the resistance training intensity: low-load/high-repetition (LL/HR) and high-load/low-repetition (HL/LR). The health status was assessed, and the primary outcomes measured were an ADL performance (ventilatory demand, ventilatory efficiency and dyspnea) and London Chest Activity of Daily Living Scale (LCADL). Secondary outcome measures were 6-minute walk distance (6MWD), isometric shoulder flexor strength and Saint George's Respiratory Questionnaire (SGRQ) scores. Results: Patients were randomly allocated to resistance training group: LL/HR (n=13) and HL/LR (n=11). The main effect of time was statistically significant in the dyspnea during ADL simulation ($p=0.005$), the LCADL physical domain ($p=0.005$), total score ($p=0.013$), and percentage of total ($p=0.039$), the 6MWD ($p=0.023$) and shoulder flexor strength ($p<0.001$). A statistically significant effect of time on SGRQ symptoms for the LL/HR group ($p=0.002$) was found. Conclusion: An equivalent improvement in ADL dyspnea and LCADL followed by improvements in exercise capacity and muscle strength were observed after both LL/HR and HL/LR. No differences were found in oxygen consumption, ventilatory demand, or efficiency after either intensities of resistance training as well as a superior effect of LL/HR training on the SGRQ symptoms domain.</p>

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