Universidade Estadual de Londrina

LETÍCIA FERNANDES BELO

DYSPNEA IN FOCUS:
INSIGHTS ON ASSESSMENT

Londrina
2023

LETÍCIA FERNANDES BELO

DYSPNEA IN FOCUS:
Insights on assessment

Tese apresentada ao Programa de Pós-Graduação em Ciências da Reabilitação (Programa Associado entre Universidade Estadual de Londrina [UEL] e Universidade Pitágoras Unopar [UNOPAR]), como requisito parcial à obtenção do título de Doutora em Ciências da Reabilitação.

Orientador: Prof. Dr. Fabio de Oliveira Pitta

Londrina
2023

Ficha de identificação da obra elaborada pelo autor, através do Programa de Geração Automática do Sistema de Bibliotecas da UEL

B452d Belo, Letícia Fernandes.
DYSPNEA IN FOCUS: Insights on Assessment / Letícia Fernandes Belo. - Londrina, 2023.
106 f. : il.

Orientador: Fabio Pitta.
Tese (Doutorado em Ciências da Reabilitação) - Universidade Estadual de Londrina, Centro de Ciências da Saúde, Programa de Pós-Graduação em Ciências da Reabilitação, 2023.
Inclui bibliografia.

1. Dyspnea - Tese. 2. Chronic Obstructive Pulmonary Disease - Tese. 3. Cardiopulmonary exercise test - Tese. 4. Locus of Symptom Limitation - Tese. I. Pitta, Fabio . II. Universidade Estadual de Londrina. Centro de Ciências da Saúde. Programa de Pós-Graduação em Ciências da Reabilitação. III. Título.

CDU 61

LETÍCIA FERNANDES BELO

DYSPNEA IN FOCUS:
Insights on assessment

A thesis submitted to the Postgraduate Program in Rehabilitation Sciences (Associated Program Universidade Estadual de Londrina [UEL] and Universidade Pitágoras Unopar [UNOPAR]), in partial fullfillment of the requeriments of the degree of Doctor in Rehabilitation Sciences.

EXAMINING COMMITTEE

_____
Prof. Fabio de Oliveira Pitta
Universidade Estadual de Londrina, Brasil

_____
Prof. Thais Rebeca Paes
Universidade Estadual de Londrina, Brasil

_____
Prof. Antenor Luiz Lima Rodrigues
St. Michaels Hospital, Toronto, Canada

_____
Prof. Carlos Augusto Marçal Camilo
Universidade Estadual de Londrina, Brasil

_____
Prof. Nidia Aparecida Hernandes
Universidade Estadual de Londrina, Brasil

Londrina, 31 de Março de 2023.

Dedico esse trabalho aos meus pais, Claudionor e Valéria, que me ensinaram a excelência de lutar da maneira que eu posso, com os recursos que eu tenho e com todas as minhas forças.

ACKNOWLEDGEMENTS

À quem me ensinou, acreditou e nunca desistiu de mim;

À quem me incentivou e me mostrou o caminho das pedras;

À quem foi exemplo, não me deixou desistir e cuidou de mim;

À quem viu o processo e me ajudou mesmo sem eu pedir ajuda;

À quem entendeu e decidiu permanecer mesmo em meio ao caos;

À quem garantiu o sorriso e a companhia durante esse processo;

À quem foi acrescentado e acrescentou muito durante caminho;

À quem me ensinou a mudar as lentes e recuperar a alegria;

À quem esteve ali, disposto e disponível para permanecer;

Meu muito obrigada.

Nominalmente agradeço,

Ao meu orientador Fabio, não existe palavras que transcrevam minha gratidão e inspiração. Obrigada por tudo, por ter aceitado tantos desafios durante esses anos.

Aos membros da banca (Profa. Nidia; Prof. Carlos; Profa. Thais; Prof. Antenor e Profa. Ercy), e suplente (Prof. Denilson), obrigada pelas contrinuições, não apenas desse momento, mas sim, durante toda a minha caminhada.

Aos mestres internacionais, especialmente Dr. Dennis, Dr. Hayley and Dr. Robert Banzett. O aprendizado não seria completo se vocês não tivessem contribuido com isso, muito obrigada pela disponibilidade e cuidado.

Aos amigos, de diferentes áreas, momentos, países e linguas, nessa pluralidade eu tive o maior suporte e alegria que poderia ter, vocês são presente de Deus e eu não os trocaria por nada.

À minha família (alguns *in memoriam*), vocês são a base de tudo e a minha certeza de que tudo vai ficar bem, mesmo em meio ao caos.

E Aquele que nunca perdeu o controle, minha razão de existência, Abba.

“Yes, we are not yet what we long to be. But we are underway”.
Stasi Eldredge

BELO, Letícia F. **Dyspnea in focus: Insights on assessment.** 2023. 106p. Thesis submitted to the Postgraduate Program in Rehabilitation Sciences (Associated Program Universidade Estadual de Londrina [UEL] and Universidade Pitágoras Unopar [UNOPAR]), – Universidade Estadual de Londrina, Londrina, 2023.

ABSTRACT

Introduction: Dyspnea is a limiting symptom in several populations, and one of the main symptoms reported by individuals with chronic obstructive pulmonary disease (COPD). The progression of dyspnea correlates with disease progression. In early stages of COPD, the complaint of dyspnea is more common during exertion, while in severe stages the subjects report a limitant sensation sometimes even at rest. In addition, dyspnea leads to impaired quality of life and hindered performance in activities of daily living. Concomitantly, a reduction in the level of physical activity in daily life increases the risk of death. In recent years there has been growing interest in the study of all facets of this symptom. However, there are still several gaps in the literature to be addressed, especially with regard to the physiological mechanisms that trigger dyspnea during exertion and its evaluation methods. **Objectives:** This thesis has the aim of contributing to the scientific evidence related to the dyspnea assessment specifically by: 1) comparing the clinical and physiological variables of individuals with and without COPD who stop exercising due to dyspnea *versus* others symptoms; and 2) making available a multidimensional tool for dyspnea assessment for Portuguese-speaking individuals with COPD. **Methodology:** Two original studies were developed: (1) The first study discriminated the proportion of individuals with and without COPD according to their reason to stop the exercise. Furthermore, the physiological responses at the peak of the exercise were verified and compared between groups, as well as their pulmonary function and clinical data; (2) In the second study, the translation, validation and reproducibility of the Portuguese version of the Multidimensional Dyspnea Profile (MDP) were proposed. **Results:** Study (1) demonstrated that, independently of COPD diagnosis, individuals who stop exercising due to dyspnea present changes such as hyperinflation and restriction of lung volumes, even with preserved exercise capacity, compared to individuals who stop for another reason. Study (2) showed that the Portuguese version of the MDP is a valid and reproducible tool for assessing this symptom in individuals with COPD. **Conclusions:** The two scientific articles contained in this thesis add novel information to the available literature on dyspnea in individuals with COPD. Rregardless of lung function, age and BMI, individuals who stop exercise due to dyspnea have greater lung restrictions than individuals who stop exercise for other reasons. Moreover, dyspnea can now be confidently assessed multidimensionally in Brazilian individuals with COPD.

Key words: Chronic Obstructive Pulmonary Disease. Dyspnea. Cardiopulmonary exercise test. Locus of Symptom Limitation. Questionnaires.

BELO, Letícia F. **Dispneia em foco: *insights* na avaliação.** 2023. 106p. Tese submetida ao curso de pós graduação em Ciências da Reabilitação (Programa associado entre a Universidade estadual de Londrina [UEL] e a faculdade Pitágoras Unopar Anhanguera [UNOPAR]) – Universidade Estadual de Londrina, Londrina, 2023.

RESUMO

Introdução: A dispneia é um sintoma limitante em diversas populações, e um dos principais sintomas relatados por indivíduos com doença pulmonar obstrutiva crônica (DPOC). A progressão da dispneia se relaciona com a progressão da doença. Em estágios iniciais da DPOC a queixa de dispneia é mais comum durante os esforços, enquanto em estágios mais avançados da doença os indivíduos podem relatar esse sintoma até mesmo ao repouso. Além disso, a presença de dispneia acarreta diminuição da qualidade de vida e limitação do desempenho nas atividades básicas de vida diária. Concomitantemente, essa redução no nível de atividade física na vida diária aumenta o risco de morte. Em décadas recentes houve um interesse crescente no estudo de todas as facetas desse sintoma. Entretanto, ainda existem várias lacunas na literatura a serem abordadas, principalmente no que concerne as alterações fisiológicas que desencadeiam esse sintoma durante o esforço e seus métodos de avaliação. **Objetivos:** A presente tese tem o intuito de contribuir com as evidências científicas relacionadas à avaliação de dispneia, especificamente por: 1) comparar as variáveis clínicas e fisiológicas dos indivíduos com e sem DPOC que param o exercício por dispneia *versus* outros sintomas; e 2) disponibilizar um instrumento multidimensional para avaliação da dispneia em indivíduos brasileiros com diagnóstico de DPOC. **Metodologia:** Dois estudos originais foram desenvolvidos: (1) O primeiro estudo discriminou a proporção de indivíduos com e sem DPOC de acordo com a razão pela qual eles pararam o exercício. Em adição, foram verificadas e comparadas as respostas fisiológicas no pico do exercício, assim como a função pulmonar e os dados clínicos dos diferentes grupos; (2) No segundo estudo foi proposta a tradução, validação e reprodutibilidade da versão em português Brasileiro do *Multidimensional Dyspnea Profile* (MDP). **Resultados:** O estudo (1) demonstrou que, independentemente do diagnóstico de DPOC, os indivíduos que param o exercício por queixa de dispneia, mesmo com uma capacidade de exercício preservada, apresentam alterações como hiperinsuflação e restrição dos volumes pulmonares mais acentuadas em relação aos indivíduos que param por outra razão. O estudo (2) mostrou que a versão em português do MDP é válida e reprodutível para a avaliação desse sintoma em indivíduos com DPOC. **Conclusões:** Os dois artigos científicos desenvolvidos agregam novas informações à literatura disponível sobre a dispneia em indivíduos com DPOC. Independente da função pulmonar, idade e IMC, indivíduos que param o exercício devido à dispneia apresentam maiores restrições pulmonares do que os indivíduos que param por outras razões. Além disso, a partir de agora a dispneia pode ser avaliada multidimensionalmente de maneira confiável em indivíduos brasileiros com DPOC.

Palavras-chave: Doença Pulmoanr Obstrutiva Crônica. Dispneia. Teste cardiopulmonar de esforço. Sintomas. Questionários.

LIST OF FIGURES

LITERATURE REVIEW

ARTICLE 1

ARTICLE 2

LIST OF TABLES

LITERATURE REVIEW

ARTICLE 1

ARTICLE 2

LIST OF ABBREVIATIONS

ATS	American Thoracic Society
BMI	Body mass Index
BORG/CR10	Borg's modified exertional scale/10 category ratio scale
CanCOLD	Canadian Cohort Obstructive Lung Disease
CAT	COPD assessment test
CHAMPS	Community Healthy Activities Model Program for Seniors
COPD	Chronic obstructive pulmonary disease
CO_2	Carbon dioxide
CPET	Cardiopulmonary exercise test
DLCO	Diffusing capacity for carbon monoxide
EELV	End-expiratory lung volume
FEV_1	Forced expiratory volume in the first second
FRC	Functional residual capacity
FVC	Forced vital capacity
GOLD	Global initiative for lung obstructive disease
HADS-A	Hospital Anxiety and Depression Scale - Anxiety
HADS-D	Hospital Anxiety and Depression Scale - Depression
HCO_3^-	Bicarbonate
HR	Heart rate
IC	Inspiratory capacity
IRV	Inspiratory reserve volume
L	Liters
LOSL	Locus of Symptom Limitation
MDP	Multidimensional Dyspnea Profile
mMRC	modified Medical Research Council
MVV	Maximal voluntary ventilation
PPO	Peak power output
Raw	Airway resistance
RV	Residual volume
SF-36	Short Form-36 version
SpO_2	Peripheral oxyhemoglobin saturation

TLC	Total lung capacity
UEL	Universidade Estadual de Londrina
UNOPAR	Universidade Pitágoras Unopar Anhanguera
V'_E	Minute Ventilation
$V'_E/V'CO_2$	Ventilatory equivalent for carbon dioxide
$V'O_2$	Oxygen uptake
V_T	Tidal Volume
W	Watts

TABLE OF CONTENT

1 INTRODUCTION

Breathing is a complex act, usually unconscious, and has a certain cost to the body (i.e., oxygen consumption) [1]. Some conditions can alter respiratory mechanisms and make the perception of breathing uncomfortable [1,2]. Chronic obstructive pulmonary disease (COPD) is an example of this. Biomechanical changes caused by the disease make the required respiratory effort greater and with higher cost than in people without the disease, even at rest [3]. Further, exercise can be described as a situation that can cause breathing discomfort in people with or without pulmonary diseases [2]. Regardless of whether dyspnea is reported as a limiting factor to exercise or during rest, it implies in hindered quality of life, emotional distress, reduction of physical activity and an increased risk of premature death [2-4]. Dyspnea is not the only reason someone stops exercising [5]. However, studies support the hyp othesis that abnormal dynamic pulmonary mechanics are likely the primary pathophysiological source of exercise intolerance in people with COPD who stop exercise because of breathlessness [6]. Nonetheless, to date, no study has examined the distribution of stopping exercise due to dyspnea in adults with and without COPD randomly sampled from the general population. Therefore, the first of the present studies has the general objective of characterizing the frequency distribution of the reasons for stopping a symptom-limited cardiopulmonary exercise test (CPET) in apparently healthy individuals and people with mild-to-very severe COPD. Also, to compare participant characteristics as well as peak physiological and perceptual responses to CPET between the groups of different reason(s) for stopping exercise.

As a symptom, dyspnea should be reported by those who feel it, and the easier way to record that is through questionnaires [2,8]. Many instruments have been developed to assess dyspnea; however, some only evaluate one dimension or aspect of this multidimensional symptom [2,9]. Because of that, the choice of evaluation method must be carefully made. The evaluator should consider the aim of the assessment (e.g., dyspnea at rest, during exercise, or response to treatment) and align it with the instrument's discriminative capacity and focus [2,8,9]. In this way, the second article of the present thesis focused on performing the translation and studying the psichometric properties of a Portuguese version of a multidimensional tool for assessment of dyspnea in individuals with COPD.

Personal statement: "I started my career as a Respiratory Physiotherapist answering the question "Why does mankind breathe?". Now, nine years after, at the last moment of my last degree in this university, I intend to clarify part of the mechanisms that interfere with that breathing pattern and cause dyspnea during exertion, as well as to discriminate assessment forms of this symptom. Thus, in line with that first question, I am trying to answer parts of the question, "Why do people feel breathless? And how to assess it?". I hope you enjoy this journey and that I achieve my objective.

Let everything that has breath praise the LORD. (Psalm 150:6a) [10]"

2 LITERATURE REVIEW – WHY DO PEOPLE FEEL BREATHLESS?

2.1 WHY DOES MANKIND BREATHE? - RESPIRATORY MECHANICS AND PHYSIOLOGY

From the Bible verse "*Then the LORD God formed man (...) and breathed into his nostrils the breath of life, and man became a living being"* (Genesis 2:7) [10], to the famous quote, *"that person took her last breath"* is possible to understand that breathing is essential to life maintenance. Breathing is something inherent to the human being. Its aim is the inhalation of oxygen and the exhalation of carbon dioxide. Thus enabling the production of energy through cellular respiration and the maintenance of the acid-base balance of the organism [1,11]. The efficiency of inspiration and expiration depends on physical variables, such as the differences in pressure between the atmosphere and the lungs, which causes the influx and outflux of air into the lungs. Although it seems simple, breathing is a complex act that requires interaction and integrity of several mechanisms. Such as, the central control, the effector organs - muscles and lungs, the transport airways, and the sensory input systems [1,11,12]. The summary of respiratory control is shown in Figure 1.

2.1.1 Central Control of Breathing

Breathing is a motor behavior, usually unconscious and involuntary, controlled by the respiratory center (medulla and pons) [1,11-13]. The dorsal medullary group controls inspiration by stimulating the diaphragm's and intercostal muscles' contraction via the phrenic and intercostal nerves (Figure 1). The

contraction leads to negative intrapulmonary pressure, generating air inflow into the lungs. Once the inspiratory stimulus ceases (dorsal medullary group activity stops), intrapulmonary pressure equals atmospheric pressure, and expiration begins. At that moment, the force of elastic recoil of the rib cage and gravity is responsible for exhalation (in regular and resting situations). On the other hand, the ventral medullary group controls forced breathing, stimulating the accessories muscles' contraction to perform a forced inspiration and/or expiration. Ventral medullary group also contains neurons responsible for rhythm generation (e.g., preBötzingre complex) [1,11,12] (Figure 1).

Pontine groupings modulate the frequency and intensity of the medullary signal through the pneumotaxic and apneustatic centers (see Figure 1 for anatomic location) [1,13]. Specifically, the pneumotaxic center coordinates the speed of breathing through inhibitory impulses to the respiratory center and is involved in the adjustments of the respiratory rate [13]. The apneustic center is responsible mainly for sending stimulatory impulses to the inspiratory area, controlling the depth of inspiration [12,13]. Prepontine regions associated with the hypothalamus and the limbic system also influence the regulation of breathing by responding to changes in internal or external environmental conditions such as exercise, hypoxia, hypercapnia, thermal changes, emotions or pain, as well as other processes like swallowing and coughing [1,14]. The limbic system and hypothalamus also provide impulses to the motor cortex during voluntary control of breathing, e.g., holding breath. Although voluntary control can be precise, it is not absolute. For example, a person cannot keep his breath forever because the accumulation of carbon dioxide will stimulate inspiration [1,13,14]. Afferences signal by sensory input systems modulates the neuronal processes above mentioned [12,14].

2.1.2 Sensory Input Systems

The sensory input systems stimulate the central respiratory organs to change the pattern or respiration intensity [12]. Either in normal circumstances, such as exercise, or abnormal situations, such as a disease, depending on metabolic demands, the sensory input system sends signals to the brain to modulate the respiratory pattern in order to regulate homeostasis [1,12]. The sensory input systems consist of mechanoreceptors, metaboreceptors, and peripheral and central chemoreceptors [1] (Figure 1).

Mechanoreceptors transmit sensory information via the vagus nerve (cranial nerve X) about the airway stretch, lung volume, and vascular congestion [12]. These receptors are placed in the airways, trachea, lungs, and pulmonary vessels and are classified as slowly or rapidly adapting. Pulmonary stretch receptors respond to volume changes and are slowly adapting. It prevents the overinflation of the lungs sending inhibitory impulses to the inspiratory center - Hering-Breuer reflex. On the other hand, rapidly adapting receptors respond to irritants, triggering defensive respiratory reflexes. Bronchopulmonary C-fiber receptors play a role as they slowly and rapidly adapt responses. Metaboreceptors are in peripheral muscles and respond to the metabolic byproducts of exercise [1,12]. Peripheral chemoreceptors are capable of detecting the change in carbon dioxide (CO_2), hydrogen ions, and significantly a decrease in oxygen (O_2) concentration (hypoxemia) [1,12,15]. Carotid bodies chemoreceptors are responsible for the more significant part of peripheral ventilation control. Aortic bodies respond to gas concentration and regulate circulation [15]. Central chemoreceptors are in the ventral surface of the medulla and the retrotrapezoid nucleus and sense primarily the

change in the pH (acidosis or alkalotic) of the cerebrospinal fluid. In healthy individuals, the respiratory center is more sensitive to acidosis than hypoxemia, which means that arterial concentration of CO_2 is the chief to determine respiration in typical situations [12,15].

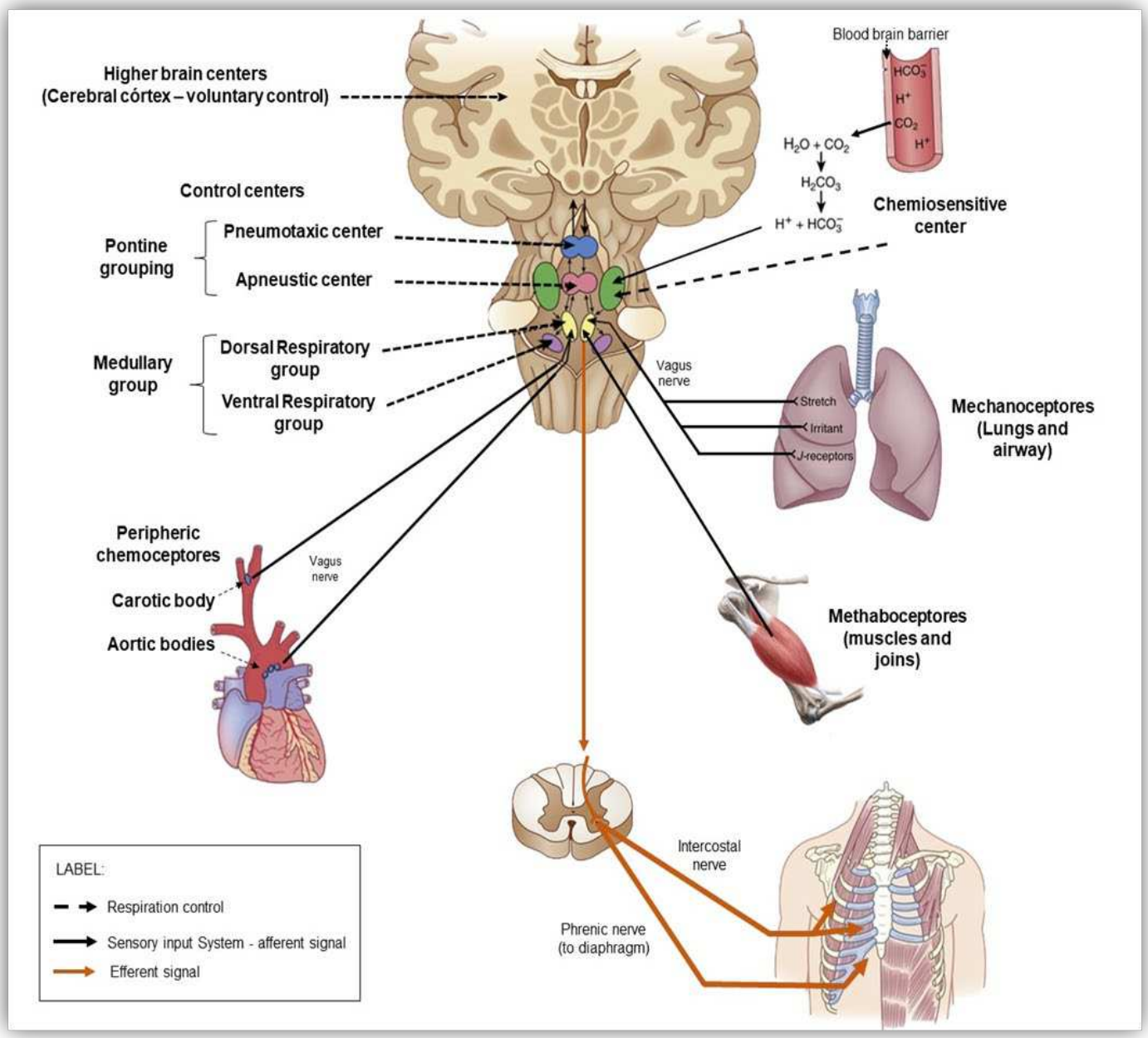


FIGURE ADAPTED BY THE AUTHOR. SOURCE: QUIZLET.COM/233042545/PULMONARY-CHAPTER-FLASH-CARDS/

Figure 1. Summary of the respiratory control system

The stimulus generated by respiratory center controls is a dose response for positive feedback, meaning the more significant the trigger, the greater the muscle response [11,15]. For example, during exercise, the consumption of oxygen and the production of CO_2 increases. In this way, the metaboreceptors and chemoreceptors send an input to the higher center to increase the motor stimuli of respiratory muscles, which respond with an increase in the speed of inspiration. If the muscle stimuli continue, the shallow inspiration will be increased to meet the body's metabolic demand. In other words, when the organism's demand is increased, the body adapts the respiratory pattern to correspond to the needs [11]. However, some situations can generate uncomplying cardiac, neuromuscular, and respiratory systems, which can result in a bad experience of respiration; called dyspnea [2,3].

2.2 What is Dyspnea?

The etymology of the word dyspnea represents what the symptom means. The term is derived from the Greek roots: *dus* and *pno*ē, which means "difficult breathing" [17]. Dyspnea is also represented by the terms dyspnoea, breathlessness, or shortness of breath. These different terms represent the same symptom. However, in everyday life, the first two ones represent a clinical description and the last two ones are more used to describe the symptom by subjects who feel it. According to the literature, the difficulty of breathing results from a mismatch between the demand of breathing and the capacity to correspond to it (neuromechanical uncoupling). Its intensity is associated with the motor command and the efferent feedback for the somatosensory areas that dyspnea activates

[2,3,18,19]. Neuroimaging studies prove that dyspnea activates cortico-limbic structures, particularly the right anterior insula and the amygdala [2,20,21]. After the COVID-19 outbreak, most of the world knows about this symptom. Nonetheless, respiratory complaints are older than respiratory pandemics. Mesopotamian hieroglyphs, dating back to 3300 BC, already had reporting words to describe respiratory discomfort [19].

Additionally, publications involving dyspnea terms can be found on Pubmed since 1800 [22,23]. Since the first reports, the symptom description has been changed. Nowadays, the American Thoracic Society (ATS) defines dyspnea as “a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity” [2,8]. The ATS statement brought the complex multidimensional nature of dyspnea sensation and the importance of its multidimensional assessment to the literature discussion. Importantly, the multidimensional nature of dyspnea means that dyspnea sensation derives from the interaction between multiple physiological, psychological, social, and environmental factors that may induce secondary physiological and behavioral responses [2].

Dyspnea is a burden that affects either healthy or people with different diseases. The prevalence of this symptom among the general population is up to 27% and increases with aging, so that the affliction rate is 15% in community-residing adults aged 40 years and 37% in subjects in the ’70s [2,19]. Also, it affects almost half of the subjects admitted to acute and tertiary care hospitals and can also be a symptom reported by subjects with cardiac and neurological disorders [23]. In subjects with chronic respiratory disease, specifically chronic respiratory obstructive disease (COPD), dyspnea is the most prevalent symptom, 73% of those subjects remain feeling breathing discomfort even with treatment [24]. In this population, this

symptom is associated with poor quality of life, reduction in physical activity, and premature death [2,7,23,24]. In this way, it is possible to perceive the importance of studying the burden of dyspnea on people with COPD.

2.2.1 Chronic Obstructive Pulmonary Disease

2.2.1.1 Definition and classification

Chronic obstructive pulmonary disease is currently defined as a heterogeneous lung condition characterized by chronic respiratory symptoms due to abnormalities of the airway that causes persistent and progressive airflow limitation [25]. The diagnosis of COPD is based on clinical evaluation and a pulmonary function test. Almost 80% of subjects diagnosed with COPD are smokers or ex-smokers, which reflects the predominance of smoking as a risk factor for developing COPD, but it is not the only one [25,26]. Other etiological factors can be pointed out, such as exposure to occupational smoke/dust, air pollution, childhood lung development, history of asthma or respiratory infection (particularly during childhood), and so forth [25]. Furthermore, the diagnosis is confirmed when the subjects present a ratio between forced expiratory volume in the first second and forced vital capacity (FEV_1/FVC) post-bronchodilator less than 70 percent. Furthermore, COPD can be classified, according to the airflow obstruction severity (expressed by the FEV_1 as a percentage of predicted), into: mild (GOLD I); moderate (GOLD II); severe (GOLD III), or very severe (GOLD IV). Beyond the obstruction classification, a combined evaluation – recently updated to GOLD ABE – which involves the symptom burden (by modified Medical Research Council [mMRC] or COPD assessment test [CAT]) and the exacerbation history is suggested. This

combined assessment is intended to assist in choosing individualized therapies and verifying the response to medication [25].

The symptoms and impairments caused by COPD increase with disease progression, which means that the clinical manifestations are more often experienced by subjects with more advanced stages of the disease. This situation can lead to the underdiagnosis of individuals with mild COPD since they present fewer or no symptoms during daily life and usually do not seek medical attention [26]. However, it is already known that people in the beginning stage of the disease present impairments that must be treated to avoid or delay the disease progression.

2.2.1.2 Pathophysiology and exercise intolerance of COPD

Since the first publication of the Global Initiative for Lung Obstructive Disease (GOLD), the term COPD encompassed a combination of two previous distinct diseases: emphysema and chronic bronchitis [25,27]. Specifically, bronchitis, which causes the narrowing of the airway, especially in small airways, and due to inflammation, mucus production is increased; and emphysema, which is characterized by the destruction of the lung parenchyma which causes the increases of death space (area with ventilation but without proper blood perfusion, not allowing gas exchange to occur). The degree of involvement by each phenotype depend on the subject affected. For example, bronchitis is a phenotype more common among women, while men usually present a predominance of emphysematous characteristics [27,28]. Besides that, biomechanical changes can increase these alterations. As an example, accessory respiratory muscles shortening and weakness deform the rib cage, causing elevation of the ribs, rectifying the diaphragmatic

cupulas, and making the incursion difficult. As a consequence of pathophysiological and biomechanical alterations, the airway resistance increases, and the lung elasticity and compliance reduce, resulting in gas trapping, known as static (at rest) and dynamic (during exercise) lung hyperinflation [1,16,29,30]. Hyperinflation is defined as an increase in end-expiratory lung volume (EELV) with a decrease in inspiratory capacity (IC) and inspiratory reserve volume (IRV), which limits the ability to expand tidal volume (V_T). All these changes induce a worse breathing experience and a ventilation/perfusion mismatch (gas exchange impairment) [2,3,30].

The prominent marks of ventilation/perfusion mismatch are the low oxygen concentration (i.e., hypoxemia) and the retention of carbon dioxide (CO_2) (i.e., persistent hypercapnia) in the bloodstream. They lead to a metabolic compensation (increase of HCO_3^-) to balance the pH disturbance [31]. This retention does not allow the proper stimulation of the dorsal respiratory group. In this way, the peripherical chemoreceptors play a role in stimulating the dorsal respiratory group in response to hypoxemia [12]. These factors, hypercapnia, and hypoxemia, increase tidal ventilation and discomfort. Hypoxemia induces rapid and shallow breaths, with higher increases in respiratory rate than tidal volume and lower oxygen cost. Acute hypercapnia generates deep and slow breaths with a relatively higher increase in tidal ventilation. It requires more significant negative pressure generation and greater oxygen consumption by respiratory muscles, which is a reason why acute hypercapnia is a more substantial stimulus for dyspnea than hypoxemia [12,30,31].

Although COPD is a respiratory disease, it does not only affect the lungs [25]. Commun systemic symptoms are body composition alteration [32], limb muscle dysfunction such as reduction of muscle mass (atrophy) and strength [33,34], decrease in exercise capacity [35,36] and physical activity level [37]. The

aforementioned impairments converge to the worsening of dyspnea sensation [3]. In turn it leads these individuals to reduce even more their activities and consequently their physical activity level, with a decrease in exercise capacity and an increase of these symptoms, and so forth. This process is characterized as the vicious cycle of COPD [38]. All these modifications contribute to exercise intolerance in COPD, which corroborates premature death in this population [25,36,38].

During exercise, the body's metabolic demands are increased. The muscles' oxygen consumption (VO_2) increases, and in this way, the mechanoreceptors, metaboreceptors, and peripheral chemoreceptors send input to the central command to increase ventilation [11]. Healthy subjects increase their V_T, decreasing their EELV, which leads to an increase in their IC, which allows tidal breathing to remain on the linear portion of the respiratory system's sigmoid pressure-volume curve. In turn, due to disease alterations, people with COPD adopt a tachypneic respiratory pattern, and often increase their EELV above resting levels when they expand their V_T in response to exercise demands. Associated gas exchange abnormalities contribute to an exaggerated V'_E response (i.e., abnormally high ventilatory equivalent for carbon dioxide [$V'_E/V'CO_2$]). This pattern contributes to dynamic hyperinflation by forcing the subjects to breathe in high volumes upper (alinear) extreme of the respiratory system sigmoid pressure-volume curve (i.e., near total lung volume where the respiratory system is non-compliant) [3]. Consequently, people with COPD have higher work of breathing to support a given level of V'_E, due to the requirement of relatively sizeable respiratory muscle pressure swings to generate any given level of V_T expansion compared with people without COPD [3,39]. This means that the respiratory system cannot correspond adequately to the stimuli sent by the central command in terms of V_T displacement, leading to the

disparity between one's central drive to breathe and their mechanical response (neuromechanical uncoupling) [2,28]. Because of that, people with COPD experience intolerable dyspnea at a much lower $V'O_2$peak than healthy subjects, a dysfunction that limits them from reaching the same exercise intensities [29].

2.2.1.3 Locus of symptom limitation

Whether in healthy people or people with COPD, exercise can be limited due to intolerable symptoms. Usually, exercise is limited by unbearable leg fatigue, intolerable breathlessness, or a combination of intolerable leg fatigue and breathlessness [5-7,40]. The literature suggests that the primary reason(s) a person with COPD stops a cardiopulmonary exercise test (locus of symptom limitation – LOSL) has the potential to (i) help predict the magnitude of response to therapy and (ii) identify the primary pathophysiological factor(s) contributing to exercise intolerance [5,41,42].

Previous literature about LOSL has not yet reached consensus about the distribution of the reasons to stop exercise in the general population and COPD. Hamilton and colleagues [5] assessed the LOSL to cardiopulmonary cycle exercise testing in healthy subjects (n=109), individuals with pulmonary disease (n=85), and people with combined pulmonary and cardiac conditions (n=107). In this study, leg fatigue was identified as the primary or co-primary reason for stopping exercise by ~90% of individuals in each group [5]. By contrast, O'Donnell and colleagues [12] reported that 84% of people with COPD (n=248) stopped cardiopulmonary cycle exercise testing due to breathlessness alone (51%) or in combination with leg fatigue (33%). In comparison, only 16% stopped due to leg

fatigue [12]. The reason for this marked discrepancy is unclear. Additional research – such as that proposed here – is needed to characterize the distribution of reasons for stopping exercise in people with mild-to-very severe COPD, and in contrast with healthy older adults.

Evidence suggests that the LOSL may provide insight into how a person with COPD responds to therapy. For example, Saey et al. [41] and Deschenes et al. [6] found that acute bronchodilation had no effect on exercise endurance time in people with COPD those whose primary or co-primary exercise-limiting symptom was leg fatigue but that it led to a clinically meaningful improvement in exercise endurance time among people with COPD reporting breathlessness (dyspnea) as their LOSL. Interestingly, in these studies, the magnitude of reduction in quadriceps twitch force (i.e., skeletal muscle fatigue) following exhaustive exercise testing was markedly higher in people with COPD who stopped exercise because of leg fatigue (alone or in combination with breathlessness vs. breathlessness alone [41,6]. The collective results of these studies (a) suggested that quadriceps contractile fatigue (skeletal muscle dysfunction) is likely the primary pathophysiological source of exercise intolerance in people with COPD reporting leg fatigue as their primary or co-primary reason for stopping exercise, and (b) supported the hypothesis that abnormal dynamic pulmonary mechanics is likely the primary pathophysiological source of exercise intolerance in people with COPD who stop exercise because of breathlessness.

Tracey et al. [42] were the first to show that people with moderate-to-very severe COPD (n=92) who reported breathlessness as their primary exercise-limiting symptom (n=34; 37%) had more significant pathophysiological abnormalities in the behavior of their dynamic operating lung volumes during exercise. Also, they

reported more unpleasant qualities of breathlessness at end-exercise than people with COPD who reported leg discomfort as their primary (n=16; 17%) or co-primary exercise-limiting symptom (n=42; 46%). More specifically, people who stop the exercise due to breathlessness present more prevalent and severe mechanical constraints on V_T expansion and dynamic lung hyperinflation during exercise than those who stop because of leg discomfort or both symptoms. This was shown by the higher magnitude of decrease in dynamic IC and the tidal volume to IC ratio (V_T%IC) at peak exercise and by the greater proportion of people classified above the thresholds of V_T%IC ≥73% and ∆IC ≥400 mL, in breathlessness group. While the results of Tracey et al. [42] supported the previous hypothesis about the significant pathophysiological abnormalities in dynamic respiratory mechanics in those who report breathlessness as their LOSL, the studies were conducted in a relatively small and homogenous group of symptomatic adults with moderate-to-very severe COPD recruited from outpatient clinics at a tertiary care medical center. Thus, it remains to be seen whether the results of Tracey et al. [42] would be similar or different in a larger group of relatively asymptomatic adults (a) with mild COPD and (b) at risk for the development of COPD randomly sampled from the general population.

2.2.1.4 Ways to assess dyspnea in COPD

It is worth emphasizing that dyspnea is a symptom (i.e., what a person says he/she is feeling) and not a sign (i.e., what the evaluator observes) which means that the subject must report their sensation [8]. The experience of dyspnea can differ between the daily life sensation (clinical dyspnea) and the

laboratory-induced sensation because the quality of the symptom can be related to the stimulus [44,45]**.** For example, the description of work/effort of breathing is more related to people with chronic respiratory diseases and during the peak of exercise. This sensation probably arises from the combination of afferent mechanoreceptor feedback and the perceived cortical motor command. In the laboratory, these descriptors appeared after the breathing stimulus in maximal voluntary hyperpnea against moderate inspiratory resistance [44]. Another example is the air hunger description; studies showed that it is related to a neuromechanical uncoupling and can provoke emotional responses (e.g., fear, anxiety, etc.) and motivate adaptative behavior (e.g., avoid some activities) [18,44]. Also, physiological and emotional factors can impact sensations and perceptions of breathlessness in people with COPD. All aspects mentioned above need to be considered by the healthcare providers during the choice of the dyspnea assessment tool [2,4,9]. The assessment tool choice is vital, as the evaluation results will guide the treatment proposal. Therefore, the treatment proposal may be wrong if the chosen instrument does not take into account the aspect of dyspnea that most affects the assessed individual.

Several instruments are available in the literature to evaluate dyspnea [8]. Some of them assess only one dimension of dyspnea, or its impact in daily life activities (e.g., mMRC [46], baseline/transition dyspnea index [47]). lthough these instruments provide useful information and are widely used worldwide, their responses are recorded based on a single moment or aspect of the symptom, therefore limiting their comprehensiveness. During the past two decades, the multidimensional assessment of dyspnea has become more common [2,8,18]. This “new” approach is more closely linked to the current understanding of the neuropathophysiology of dyspnea and takes into consideration the sensory (intensity

and qualities), affective (unpleasantness or distress), and impact burden of dyspnea on the activity of daily living [2,8,9,18,44,45]. Once different descriptions of respiratory discomfort are related to other pathophysiological mechanisms [2,18], the evaluators have a better overview of the aspects that cause this symptom and propose more effective treatment strategies. The dyspnea consensus described the instruments that assess dyspnea, either specifically or with one item of its context (mainly in English as original language). Recently, Willians [9] and Lewthwaite et al. [48] summarized the standardized instruments, specific developed to evaluate dyspnea, at rest and during exercise. Table 1 presents a list of the instruments available in Portuguese that assess dyspnea in people with COPD.

Table 1. Summary of clinical specific and non-specific instruments to assess dyspnea.

Assessment tool	N°. of items	Dyspnea dimensions assessed				Use
		SI	SQ	UN/AD	ID*	
Specific						
Baseline Dyspnea Index [47]	3	-	-	-	X	Rest
Borg Scale CR10 [49]	1*	X	-	X	-	Rest/Exercise
Dyspnoea-12 [50]	12	-	X	X	-	Rest/Exercise
Dyspnea Management Questionnaire [51]	30	-	-	X	X	Rest
modified Medical Research Council [46]	1	-	-	-	X	Rest
Multidimensional Dyspnea Profile [52]	11	X	X	X	-	Rest/Exercise
Numerical Rating Scale [53]	1*	X	-	X	-	Rest/Exercise
Transition dyspnea Index [47]	3	-	-	-	X	Rest
Visual Analogue Scale [54]	1*	X	-	X	-	Rest/Exercise
Non-specific	**Dyspnea's Items**					
Chronic Respiratory Disease Questionnaire [55]	5	-	-	-	X	Rest
Clinical COPD Questionnaire [56]	8	-	-	-	X	Rest
COPD Assessment Test [57]	1	X	-	-	X	Rest
London Chest Activity of Daily Living Scale [58]	15	-	-	-	X	Rest
Pulmonary Functional Status & Dyspnea Questionnaire_modified [59]	10	X	-	-	X	Rest
Saint George's Respiratory Questionnaire [60]	3	-	-	-	X	Rest
Seattle Obstructive Lung Questionnaire [61]	18	X	-	-	X	Rest

*Number of items dependent on how many different domains of breathlessness assessed. SI: sensory intensity; SQ: sensory quality; UN/AD: unpleasantness/affective distress; ID: indirect; CR10: 0–10 category ratio scale.

Table 1 shows that the Multidimensional Dyspnea Profile (MDP) assessed sensory quality, intensity and unpleasantness of dyspnea. It was constructed based on physiological correlations and has been used to detect different sensations of breathlessness in many contexts, such as laboratory experiments, exercise and emergency rooms [52,62]. The dyspnea descriptors reported in the MDP are similar to the ones used to describe respiratory discomfort by Brazilians with COPD, which could facilitate the validation of this instrument used in Brazil [63]. However, until 2019 this instrument was available only in English and French, which made it impossible to use in Portuguese-speaking countries such as Brazil. Because of that unavailability, the second article of this thesis was developed.

2.3 THESIS' OBJECTIVES

Article 1

1) To characterize the frequency distribution of the reasons for stopping symptom-limited cardiopulmonary cycle exercise testing (CPET) in people with mild-to-very severe COPD and in apparently healthy individuals (ever smokers without spirometric evidence of COPD).

2) To compare participant characteristics as well as peak physiological and perceptual responses to CPET between people who report breathlessness, leg discomfort, or a combination of breathlessness and leg discomfort as their reason(s) for stopping exercise.

Article 2

To provide a Portuguese version of the Multidimensional Dyspnea Profile, investigating its validity and reliability in Brazilian patients with COPD.

2.4 REFERENCES OF THE LITERATURE REVIEW

1. West JB, Luks AM. West's respiratory physiology: the essentials. 10th ed. Philadelphia: Wolters Kluwer; 2016.
2. Parshall MB, Schwartzstein RM, Adams L, Banzett RB, Manning HL, Bourbeau J, et al. An official American thoracic society statement: update on the mechanisms, assessment, and management of dyspnea. Am. J. Respir. Crit. Care Med. 2012; 185: 435–452.
3. O'Donnell, D.E., et al., Pathophysiology of dyspnea in chronic obstructive pulmonary disease: a roundtable. Proc Am Thorac Soc, 2007. 4(2): 145-68.
4. Janssen DJ, Wouters EF, Spruit MA. Psychosocial consequences of living with breathlessness due to advanced disease. Curr Opin Support Palliat Care 2015; 9: 232–37.
5. Hamilton, A.L., et al., Symptom intensity and subjective limitation to exercise in patients with cardiorespiratory disorders. Chest, 1996. 110(5): 1255-63.
6. Deschenes, D., et al. Locus of symptom limitation and exercise response to bronchodilation in chronic obstructive pulmonary disease. J Cardiopulm Rehabil Prev, 2008; 28(3): 208-14.
7. Bodegard, J., et al. Reason for terminating an exercise test provide independent prognostic information: 2014 apparently health men followed for 26 years. Eur Heart J, 2005; 26:1394-1401.
8. American Thoracic Society. Dyspnea: mechanisms, assessment, and management. A consensus statement. Am J Respir Crit Care Med 1999; 159: 321–40.

9. Williams MT, Johnston KN. Multidimensional measurement of breathlessness: recent advances. Curr Opin Support Palliat Care 2019; 13: 184–92.
10. Holy Bible, New International Version®, Publisher Biblica, Inc, 2011.
11. Mortola JP. How to breathe? Respiratory mechanics and breathing pattern. Respir Physiol Neurobiol. 2019; 261: 48-54.
12. Brinkman JE, Toro F, Sharma S. Physiology, Respiratory Drive. In: StatPearls Treasure Island (FL): StatPearls Publishing; 2022; PMID: 29494021 https://www.ncbi.nlm.nih.gov/books/NBK482414/?report=printable.
13. Dutschmann M, and Dick TE. Pontine Mechanisms of Respiratory Control. Compr Physiol. 2012; 2: 2443–69.
14. Fukushi I, Yokota S, Okada Y. The role of the hypothalamus in modulation of respiration. Resp Physio and Neurobiol. 2019; 265: 172-9.
15. Adler D, Janssens JP. The Pathophysiology of Respiratory Failure: Control of Breathing, Respiratory Load, andMuscle Capacity. Respiration. 2019; 97(2): 93-104.
16. Sue DY. Measurement of lung volumes in patients with obstructive lung disease. A matter of time (constants). Ann Am Thorac Soc. 2013; 10(5): 525-30.
17. Oxford Languages Dictionary [online]. Accessed 11/11/2022 https://languages.oup.com/google-dictionary-en/.
18. Laviolette L, Lavenziana P. Dyspnoea: a multidimensional and multidisciplinary approach. Eur Respir J. 2014; 43: 1750–62.
19. Mahler DA. Evaluation of dyspnea in the elderly. Clin Geriatr Med. 2017; 33(4): 503-21.

20. Evans KC, Banzett RB, Adams L, McKay L, Frackowiak RS, Corfield DR. Bold fMRI identifies limbic, paralimbic, and cerebellar activation during air hunger. J Neurophysiol 2002; 88: 1500–11.
21. von Leupoldt A, Sommer T, Kegat S, et al. Dyspnea and pain share emotion-related brain network. Neuroimage. 2009; 48(1) :200–6.
22. PubMed advanced search. Accessed 11/11/2022 https://pubmed.ncbi.nlm.nih.gov/?term=%28dyspnea%29+OR+%28dyspnoea%29+OR+%28breathlessness%29.
23. Bausewein C, Schunk M, Schumacher P, Dittmer J, Bolzani A, Booth S. Breathlessness services as a new model of support for patients with respiratory disease. Chron Repir Dis. 2018; 15(1): 48-59.
24. Sundh J, Ekström M. Persistent disabling breathlessness in chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis 2016; 11: 2805–12.
25. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease 2023 REPORT. Available from www.goldcopd.org.
26. Adeloye D, Song P, Zhu Y, Campbell H, Sheikh A, Rudan I. Global, regional, and national prevalence of, and risk factors for, chronic obstructive pulmonary disease (COPD) in 2019: a systematic review and modelling analysis. Lancet Respir Med. 2022; 10: 447-58.
27. Marsh SE, Travers J, Weatherall M, et al. Proportional classifications of COPD phenotypes. Thorax. 2008; 63(9):761-7.

28. Aryal, S., Diaz-Guzman, E. & Mannino, D. M. Influence of sex on chronic obstructive pulmonary disease risk and treatment outcomes. Int J Chron Obs. Pulmon Dis. 2014; 9:1145–54.
29. Costi S, Crisafulli E, Antoni FD, Beneventi C, Fabbri LM, et al. Effects of unsupported upper extremity exercise training in patients with COPD: a randomized clinical trial. Chest. 2009; 136: 387-95.
30. O'Donnell DE, Laveneziana P. Physiology and consequences of lung hyperinflation in COPD. Eur Respir Rev 2006; 15(100): 61-7.
31. Csoma B, Vulpi MR, Dragonieri S, Bentley A, Felton T, Lazar Z, et al. Hypercapnia in COPD: Causes, consequences, and therapy. J. Clinc Med. 2022; 11, 3180.
32. Machado FVC, Schneider LP, Fonseca J, Belo LF, Bonomo C, Morita AA, et al. Clinical impact of body composition phenotypes in patients with COPD: a retrospective analysis. Eur J Clin Nutr. 2019; 73, 1512-9.
33. Mathur S, Brooks D, Carvalho CR. Structural alterations of skeletal muscle in copd. Front Physiol. 2014; 5, 104.
34. Maltais F, Decramer M, Casaburi R, Barreiro E, Burelle Y, Debigaré R, et al. An official American Thoracic Society/European Respiratory Society statement: update on limb muscle dysfunction in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2014; 189(9):e15-62.63.
35. Oga T, Nishimura K, Tsukino M, Sato S, Hajiro T, Mishima M. Exercise capacity deterioration in patients with COPD: longitudinal evaluation over 5 years. Chest, 2005. 128(1): 62-9.

36. Oga T, Nishimura K, Tsukino M, Sato S, Hajiro T. Analysis of the factors related to mortality in chronic obstructive pulmonary disease: role of exercise capacity and health status. Am J Respir Crit Care Med. 2003; 167(4): 544-9.

37. Pitta F, Troosters T, Spruit MA, Probst VS, Decramer M, Gosselink R. Characteristics of physical activities in daily life in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2005; 171(9): 972-7.

38. Ramon, M. A., Ter Riet, G., Carsin, A. E., Gimeno-Santos, E., Agusti, A., Anto, J. M., et al. The dyspnoea-inactivity vicious circle in COPD: development and external validation of a conceptual model. Eur Respir J. 2018; 52(3), 1800079.

39. O'Donnell DE. Hyperinflation, dyspnea, and exercise intolerance in chronic obstructive pulmonary disease. Proc Am Thorac Soc. 2006; 3(2): 180–4.

40. Killian, K.J., et al. Exercise capacity and ventilatory, circulatory, and symptom limitation in patients with chronic airflow limitation. Am Rev Respir Dis, 1992. 146(4): 935-40.

41. Saey, D., et al. Contractile leg fatigue after cycle exercise: a factor limiting exercise in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2003; 168(4): 425-30.

42. Tracey L, Lewthwaite H, Abdallah SJ, Murray S, Wilkinson-Maitland CA, Donovan A, et al. Physiological and perceptual responses to exercise according to Locus of symptom limitation in COPD. Respir Physiol Neurobiol. 2020; 273: 103322.

43. O'Donnell, D.E., et al., Reliability of ventilatory parameters during cycle ergometry in multicentre trials in COPD. Eur Respir J, 2009. 34(4): 866-74.

44. Banzett RB, Pedersen SH, Schwartzstein RM, Lansing RW. The affective dimension of laboratory dyspnea: air hunger is more unpleasant than work/effort. Am J Respir Crit Care Med. 2008; 177: 1384-90.

45. Williams MT, Lewthwaite H, Paquet C, Johnston K, Olsson M, Belo LF, et al. Dyspnoea-12 and Multidimensional Dyspnea Profile: systematic review of use and properties. J Pain Symp Manage. 2022; 63(1):e75-e87.

46. Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. Thorax.1999; 54: 581-6.

47. Mahler DA, Weinberg DH, Wells CK, Feinstein AR. The measurement of dyspnea. Contents, interobserver agreement, and physiologic correlates of two new clinical indexes. Chest. 1984; 85: 751-8.

48. Lewthwaite H, Koch EM, Tracey L, Jensen D. Curr Opin Support Palliat Care. 2019; 13:152-60.

49. Borg GA. Psychophysical bases of perceived exertion. Med Sci Sports Exerc. 1982; 14:377–381.

50. Yorke J, Moosavi SH, Shuldham C, Jones PW. Quantification of dyspnoea using descriptors: development and initial testing of the dyspnoea-12. Thorax. 2010; 65: 21–6.

51. Migliore Norweg A, Whiteson J, Demetis S, Rey M. A new functional status outcome measure of dyspnea and anxiety for adults with lung disease: The Dyspnea Management Questionnaire. J Cardiopulm Rehabil. 2006; 2006: 395-404.

52. Banzett RB, O'Donnell CR, Guilfoyle TE, et al. Multidimensional dyspnea profile: an instrument for clinical and laboratory research. Eur Respir J. 2015; 45: 1681–91.

53. Gift AG, Narsavage G. Validity of the numeric rating scale as a measure of dyspnea. Am J Crit Care. 1998; 7: 200–4.

54. Aitken RC. Measurement of feelings using visual analogue scales. Proc R Soc. Med. 1969; 62: 989–93.

55. Guyatt GH, Berman LB, Townsend M, Pugsley SO, Chambers LW. A measure of quality of life for clinical trials in chronic lung disease. Thorax. 1987; 42: 773-8.

56. van der Molen T, Willemse B, Schokker S, ten Hacken N, Postma D, Juniper E. Development, validity and responsiveness of the Clinical COPD Questionnaire. Health Qual Life Outcomes. 2003; 1:13.

57. Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD assessment test. Eur Respir J. 2009; 34: 648-54.

58. Garrod R, Bestall JC, Paul EA, Wedzicha JA, Jones PW. Development and validation of a standardized measure of activity of daily living in patients with severe COPD: The London Chest Activity of Daily Living scale (LCADL). Respir Med. 2000; 94: 589-90.

59. Lareau SC, Meek PM, Roos PJ. Development and testing of the modified version of the pulmonary functional status and dyspnea questionnaire (pfsdq-m). Heart Lung. 1998; 27:159-68.

60. Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure of health status for chronic airflow limitation. The St. George's respiratory questionnaire. *Am Rev* Respir Dis. 1992; 145: 1321-7.

61. Tu S-P, McDonell MB, Spertus JA, Steele BG, Fihn SD, Ambulatory Care Quality Improvement Project Investigators. A new self-administered questionnaire to monitor health related quality of life in patients with COPD. Chest. 1997; 112: 614-22.

62. Meek PM, Banzett R, Parsall MB, et al. Reliability and validity of the multidimensional dyspnea profile. Chest. 2012; 141: 1546–53.

63. Teixeira CA, Júnior ALR, Straccia LC, Vianna ESO, Silva GA, Martinez JAB. Dyspnea descriptors developed in Brazil: application in obese patients and in patients with cardiorespiratory diseases. J Bras Pneumol. 2011; 37(4): 446-54.

3 ARTICLE 1

Title: Locus of symptom limitation to cardiopulmonary exercise testing in people with COPD and in healthy older adults: Physiological determinants and association with clinical and patient-reported outcomes.

Formatted according to the journal: Annals of the American Thoracic Society – Impact Factor: 8.785

Authors: Letícia F. Belo[1,2,3], Hayley Lewthwaite[1,4], Benjamin M. Smith[5,6], Jean Bourbeau[5,6], Fabio Pitta[2], Dennis Jensen[1,5,6,7]; on behalf of the CanCOLD Collaborative Research Group and the Canadian Respiratory Research Network (CRRN).

Affiliations

[1] Clinical Exercise & Respiratory Physiology Laboratory, Department of Kinesiology and Physical Education, McGill University, Montréal, QC, Canada.

[2] Laboratory of Research in Respiratory Physiotherapy (LFIP), Department of Physiotherapy, State University of Londrina (UEL) - Londrina (Brazil).

[3] Universidade Pitágoras Unopar Anhanguera – Londrina (Brazil)

[4] Innovation, IMPlementation and Clinical Translation in Health (IIMPACT), University of South Australia, Adelaide, South Australia, Australia.

[5] Research Institute of the McGill University Health Centre, Translational Research in Respiratory Diseases Program, Montréal, QC, Canada.

[6] Division of Respiratory Medicine, Faculty of Medicine, McGill University, Montréal, QC, Canada.

[7] Research Centre for Physical Activity and Health, Faculty of Education, McGill University, Montréal, QC, Canada.

Corresponding author

Dennis Jensen, PhD

Department of Kinesiology and Physical Education 475 Pine Avenue West, Montreal, QC, Canada H2W 1S4

Phone: +1 514 398-4184

Email: dennis.jensen@mcgill.ca

Authors contributions

Conception and design: LFB, HL, DJ; Data collection: BMS, JB; Analysis and interpretation: LFB, HL, DJ; Drafting the manuscript: LFB, HL, FP, JD; Revising the manuscript and final approval: all authors.

Funding information

The Canadian Cohort Obstructive Lung Disease (CanCOLD; NCT00920348) is currently funded by the Canadian Respiratory Research Network, the Canadian Institutes of Health Research (CIHR; CIHR/Rx&D Collaborative Research Program Operating Grants- 93326), and the industry partners AstraZeneca Canada Ltd, Boehringer Ingelheim Canada Ltd, GlaxoSmithKline (GSK) Canada Ltd, and Novartis. Previous funding partners were the Respiratory Health Network of the Fonds de la recherche en santé du Québec (FRQS), the Foundation of the McGill University Health Centre, and industry partners: Almirall; Merck, Nycomed; Pfizer Canada Ltd; and Theratechnologies. LFB was supported by an individual scholarship by CAPES (*Coordenação de Aperfeiçoamento de Pessoal de Nível Superior)*, Brazil.

Running title: Reasons for stopping exercise: physiological implications

Descriptor number: 8.13: Exercise in health & Disease.

Word count: manuscript: 3022 word / abstract: 248 words

This article has a data supplement, which is accessible from this article's home page (In the text the supplementary tables are represented with the letter E).

For a better reading flow, all figures and tables are displayed at the results section, although this does not correspond to the journal format. Also, to clarify the understanding about the sample, a paragraph about CanCOLD study was added in the methods section. This paragraph will not be part of the paper final version

ABSTRACT

Rationale: The locus of symptom limitation (LOSL) may reflect the primary pathophysiological factor contributing to exercise intolerance in individuals with chronic obstructive pulmonary disease (COPD) and in healthy subjects. However, the distribution of LOSL and the physiological exercise responses according to it are not described yet in a population-based sample study.

Objectives: To characterize the frequency distribution of the LOSL to symptom-limited incremental cycle cardiopulmonary exercise test (CPET) in individuals with mild-to-very severe COPD and in apparently healthy older adults; and to compare participant characteristics as well as physiological and perceptual responses to CPET between the LOSL groups.

Methods: Data from 1,225 subjects with and without COPD who participated of the baseline visit of the Canadian Cohort Obstructive Lung Disease were analyzed. The CPET peak responses were compared between five LOSL groups (breathlessness, leg discomfort, both, general fatigue and other). Adjusted analysis was run to verify the influence of covariables on exercise responses between groups.

Measurements and Main Results: The majority of participants report leg discomfort as their LOSL (n=521, 42%), breathlessness was the fourth reason chosen (n=170, 13%). Breathlessness LOSL group presented higher exercise capacity than leg discomfort (adjusted mean (95%CI) PPO: 13.64 (6.40, 20.89), $V'O_2$: 0.13 (0.02, 0.23), respectively, P≤0.009). However, they had greater inspiratory constrains restrictions and worse breathing reserve than the other groups.

Conclusions: Despite having better exercise capacity, subjects who stop exercise due to breathlessness present worse pulmonary impairments at the peak of exercise when compared with those who stopped for other reasons.

Key words: Exercise tolerance; Dyspnea; Symptom Assessment; COPD.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a prevalent chronic health condition characterized by high symptom burden (particularly breathlessness) and exercise intolerance. The level of exercise intolerance for people with COPD has important implications for prognosis; as an example, it is a better predictor of adverse health outcomes including risk of hospitalisation and premature death compared to measures of airflow obstruction (i.e., forced expiratory volume in 1-sec) (2,3). Cardiopulmonary exercise testing (CPET) is the gold standard for assessing exercise capacity and factors contributing to exercise intolerance (4). Importantly, CPET provides the opportunity to obtain data on patients' primary reason for stopping maximal exercise, or their 'locus of symptom limitation' (LOSL) (4,5). The LOSL is commonly categorized into 'breathlessness', 'leg discomfort', or a combination of breathlessness and leg discomfort (i.e., 'both') (5-6).

A growing body of evidence suggests the LOSL has the potential to help identify the primary pathophysiological factor(s) contributing to exercise intolerance, and therefore, may help to predict responses to different therapeutic approaches (6, 7). For example, people with COPD who reported leg discomfort as their primary or co-primary reason for stopping exercise were shown to have quadriceps contractile fatigue (skeletal muscle dysfunction) as the primary pathophysiological mechanism for exercise intolerance and did not improve their endurance time in response to bronchodilator therapy (6,7). In contrast, those who reported breathlessness as their LOSL had greater ventilatory limitation at the peak of exercise (8) and demonstrated a greater improvement in endurance time in response to bronchodilator therapy (7).

Despite the emerging evidence around the applicability of the LOSL, the expected distribution of LOSL across the spectrum of COPD status, from no

spirometric evidence of COPD to severe COPD, has not yet been well established or characterized. Hamilton et al. (9) found that independent of underlying medical condition (healthy, pulmonary disease alone or combined with cardiac conditions), almost 85% of subjects reported leg discomfort as their LOSL. However, O'Donnell et al. (10) reported people with COPD were most limited by breathlessness alone (LOSL: breathlessness alone=51% *vs* breathing and leg discomfort=33% *vs* leg discomfort alone 16%). The reason for these differences is not clear, although, the specific sampling approaches used (patients referred for CPET (9) or included in other randomised trials (10)) may play a role. Additional studies from population-based samples and apparently healthy subjects should help to explain these inconsistencies. Also, it remains to be understood whether the results above mentioned would be similar in a larger group of relatively asymptomatic adults with mild COPD and at risk for the development of COPD randomly sampled from the general population.

For these reasons the present study aimed to: 1) characterize the frequency distribution of the LOSL to symptom-limited incremental cycle CPET in people with mild-to-very severe COPD and in apparently healthy adults (never or ever smokers without COPD); and 2) compare participant characteristics as well as peak physiological and perceptual responses to CPET between people who report breathlessness, leg discomfort, both, general fatigue or other reason as their LOSL. The hypothesis was that people reporting breathlessness as their LOSL will have (a) worse clinical and patient reported outcomes and (b) more prevalent and severe mechanical constraints on V_T expansion and dynamic lung hyperinflation during exercise compared with people reporting leg discomfort as their primary or co-primary LOSL.

MATERIAL AND METHODS

Study design and information about CanCOLD

The present study is a cross-sectional analysis of data from the initial assessment visit of the Canadian Cohort Obstructive Lung Disease (CanCOLD) study (ClinicalTrials.gov: NCT00920348). CanCOLD is a prospective longitudinal cohort study, with participants recruited from across nine sites in Canada through random digit dialing (landline). The CanCOLD sample is composed by subjects with COPD and subjects with normal post-bronchodilator spirometry (ever smoker for those at-risk and never-smoker for the healthy controls), matched for sex and age. Assessments occur at baseline, 18 months, 3 years and beyond. In each site, technicians are trained beforehand and certified with respect to study procedures. Quality of assessments was evaluated by each site and monitored by a coordination center. Protocol details about participant eligibility and measurement techniques have been previously reported (11).

Participants

Participants of CanCOLD were classified into four groups according to their tobacco smoking and/or COPD status, defined by the global initiative for chronic lung disease (GOLD) (1): 1) never smokers without COPD; 2) ever smokers without COPD; 3) mild COPD; and 4) moderate-to-severe COPD. All participants across CanCOLD groups were included in the present study if they performed cardiopulmonary exercise testing and had: 1) physiological response data available at peak exercise and 2) the reason(s) for stopping exercise.

Measurements

Participants completed a structured interview with a trained researcher, providing information on basic sociodemographic data and health information. Standing height and body mass were also assessed. Specific questionnaires were used to assess: activity-related breathlessness (Medical Research Council dyspnea scale [MRC] (12)); physical activity levels (Community Healthy Activities Model Program for Seniors [CHAMPS] (13)); health status (general: Short Form-36 version [SF-36] (14); and disease-specific: COPD Assessment Test [CAT] (15)) and psychosocial symptoms (Hospital Anxiety and Depression Scale [anxiety: HADS-A; depression: HADS-D] (16)). Spirometry (pre-post bronchodilator), pulmonary diffusing capacity for carbon monoxide and lung volumes via body plethysmography were assessed according to standard techniques (17-19) and specific reference values were used (20).

Cardiopulmonary exercise test

Protocol

Symptom-limited incremental CPET was performed on an electronically braked cycle ergometer according to recommended guidelines (21). The CPET protocol consisted of a steady-state rest period of at least 6 minutes, followed by 1-min of unloaded pedaling (warm-up) and then 10 $W \cdot min^{-1}$ increases in power output (starting at 10 W) until symptom limitation. Gas exchange and breathing pattern parameters were collected breath-by-breath using a computerized CPET system; subjects breathed through a mouthpiece and low resistance flow transducer. Nasal passages were occluded with a nose clip. 12-lead electrocardiogram assessed heart

rate and rhythm; peripheral oxyhemoglobin saturation (SpO_2) was monitored by finger pulse oximetry. At rest, every two minutes during CPET, and at peak exercise, maximal IC maneuvers were performed, blood pressure was assessed, and intensity ratings of perceived breathlessness and leg discomfort were captured using the 0-10 modified Borg scale (22).

Locus of symptom limitation

At end exercise, participants were asked to identify their reason for stopping exercise, selecting from breathlessness, leg discomfort, a combination of breathlessness and leg discomfort or other. Participants who selected “other” were asked to provide a LOSL, which was recorded verbatim. For the purpose of the current study, responses in the other LOSL category were dichotomised into general fatigue and other.

Analysis of exercise end points

Physiological parameters were averaged over the last 30-sec of loaded pedaling and linked with simultaneous symptom intensity ratings and IC-derived parameters, including inspiratory reserve volume (IRV = IC peak minus the concomitant 30-sec averaged V_T). Peak physiological responses to CPET were expressed in relation to reference values, recently developed from the CanCOLD cohort (23). Peak minute ventilation (V'_E) was also expressed relative to the estimated maximal voluntary ventilation (MVV) (calculated as forced expiratory volume in 1-sec [FEV_1] x 35) (18).

Statistical Analysis

Participants were described by basic sociodemographic characteristics, health status and peak physiological and symptom responses to CPET according to LOSL group. Due to the non-normality distribution assessed by the Shapiro-Wilk test, the data were described as a median and interquartile range [25-75%], or otherwise as indicated. Kruskal Wallis test with Bonferroni post-hoc evaluated differences between LOSL groups for: 1) participant characteristics (socio-demographic, pulmonary function test parameters, health status) and 2) physiological and perceptual responses at the symptom-limited peak of CPET. The Chi-square test was used to compare the proportion of the participants classified according to the thresholds for breathing reserve (peak ventilation/estimated maximal ventilatory ratio [V'_E%MVV] ≥85%); ventilatory inefficiency ($V'_E/V'CO_2$ nadir ≥34) and inspiratory constrains (V_T%IC ≥73%; ΔIC from rest ≥150 ml and IRV ≤70ml) (23-26). Posteriorly, general linear models with Bonferroni post-hoc test estimated differences in physiological and perceptual responses to CPET between LOSL groups. Models were estimated unadjusted and adjusted for participant age, sex, height, body mass, cigarette pack-years, FEV_1 (L) and RV (%TLC). The adjusted data are described as adjusted mean (95% confidence interval) and standard error. For all analyses, a P-value <0.05 was considered as statistically significant. Statistical analyses were performed using the Statistical Package of Social Sciences (version 24.0, SPSS Inc., USA). Also, the same analyses were done to evaluate the difference between subjects with and without COPD diagnosis according to their LOSL. In the tables, the difference between groups are labeled as 1 for breathlessness; 2 for leg discomfort; 3 for other; 4 for general fatigue; and 5 for other group.

RESULTS

Out of the 1,247 subjects who participated in visit 1 of CanCOLD, 1,225 (98%) had complete CPET and LOSL data and were therefore included in the final analysis (Figure 1). They were 698 (57%) men, on average 66±9 years old with a body mass index of 27.4±4.9 Kg/m^2 and FEV_1 92±19 %predicted.

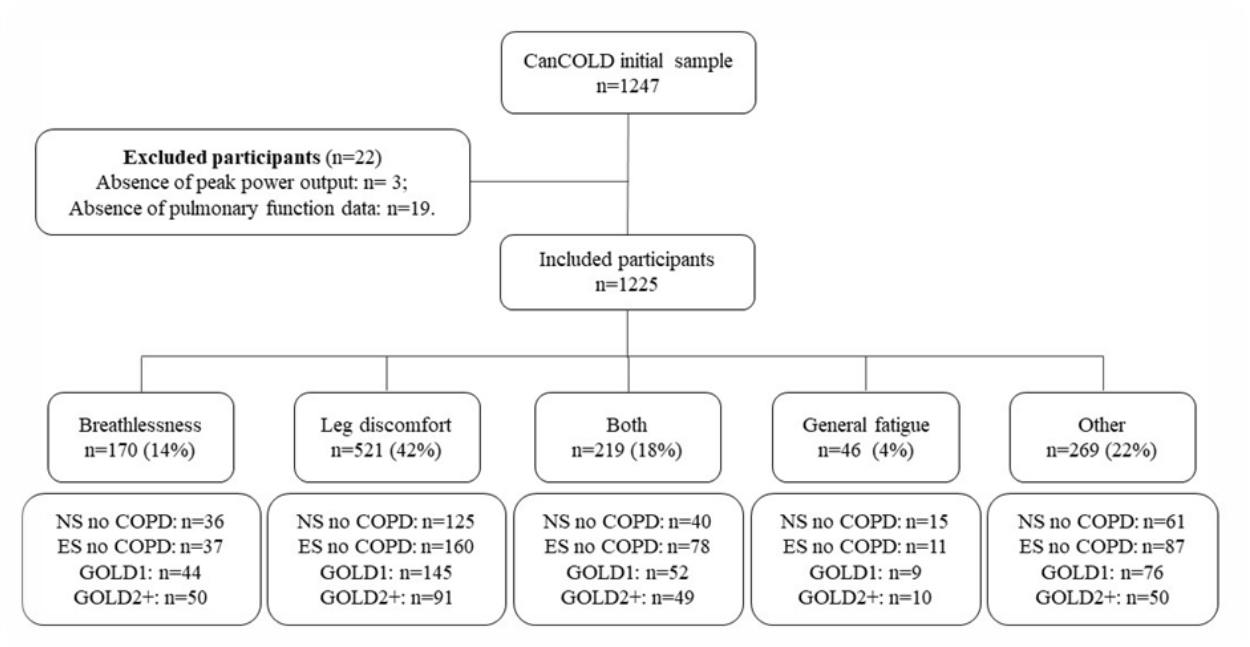


Figure 1. Participants' flow diagram.
Legend: CanCOLD: Canadian Cohort Obstructive Lung Disease NS no COPD: never smokers without COPD; ES no COPD: ever smokers without COPD; GOLD1: subjects with mild COPD and GOLD2+: subjects with moderate-very severe COPD.

Distribution and characterization of LOSL

The number and participants' proportion in each of the LOSL groups is presented in Figure 1. 'Leg discomfort' alone was the most commonly reported LOSL, reported by 521 (42%) participants. There were 219 (18%) participants who reported a combination of 'breathlessness' and 'leg discomfort' and 170 (13%) who reported 'breathlessness' alone. 'Other' LOSL was reported by 296 (22%) of

participants, with common descriptions including medical condition, unable to maintain pedaling, equipment discomfort/problem and dry throat. Few participants reported 'general fatigue' (n=46, 4%).

Within each LOSL group, the number and proportion of participants according to CanCOLD COPD status are presented in Figure 1 and Figure 2B, and according to COPD diagnosis in Figure 2C. 'Leg discomfort' was the most commonly reported LOSL across each of the CanCOLD COPD status groups (no COPD never smoker n=125, 45%; no COPD ever smoker n=160, 43%; mild COPD n=145, 44%; moderate-to-severe COPD n=91, 20%). However, 'breathlessness' was most often reported as the LOSL by people with COPD (according to CanCOLD COPD status and diagnosis) compared to without COPD (56% vs 44 %, respectively) (Figure 2).

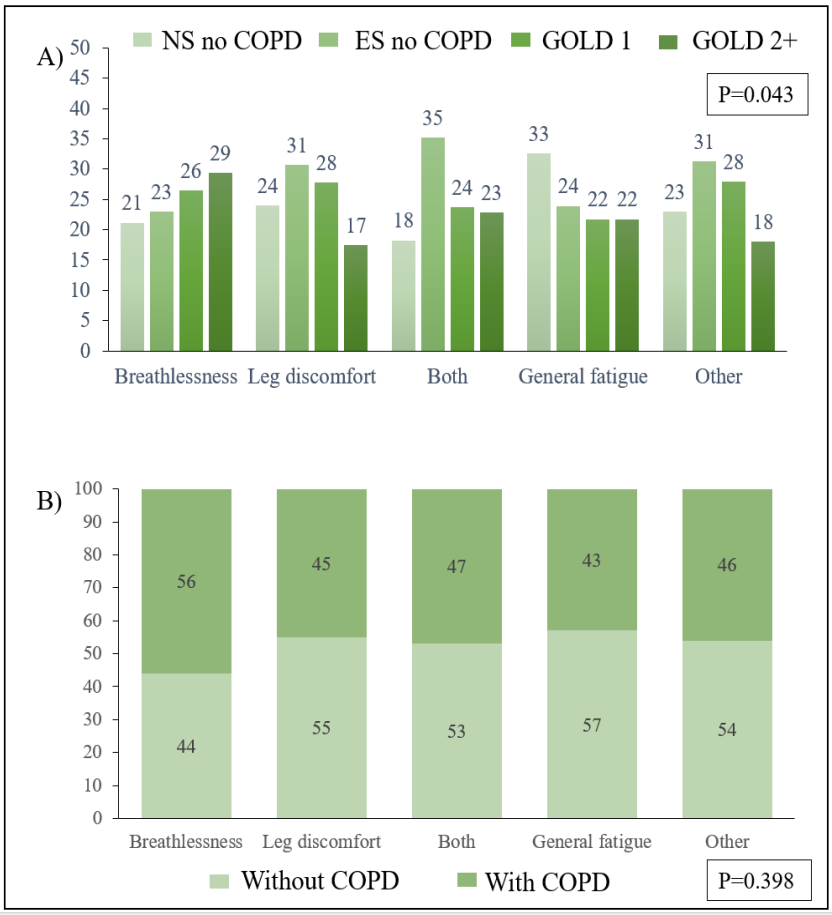


Figure 2. Frequency distribution of the population through CanCOLD groups in panel A and COPD diagnosis in panel B, according to locus of symptom limitation.
Legend: NS no COPD: never smokers without COPD; ES no COPD: ever smokers without COPD; GOLD1: subjects with mild COPD and GOLD2+: subjects with moderate-very severe COPD.

Despite a similar proportion of participants with and without a COPD diagnosis in each of the LOSL groups (Table 1 and Figure 2B), the ‘breathlessness’ group had significantly lower FEV_1 (L and %predicted) compared to the ‘leg discomfort’ and ‘other’ groups, and a significantly lower FVC (L and %predicted) and residual volume (%TLC) compared to the ‘other’ group ($P \leq 0.009$).

There were no significant differences between the LOSL groups for other demographic data, self-reported medical conditions, or 12-month exacerbation/hospitalization history (Table 1). According to symptom burden, participants in the ‘breathlessness’ LOSL group had more COPD-specific symptoms (assessed via the CAT) compared to those in the ‘other’ group ($P \leq 0.01$). However, they self-reported higher physical activity levels compared to the ‘general fatigue’ group ($P \leq 0.03$). Other differences in participants’ characteristics and symptom burden can be found in Table 2.

Table 1. Pulmonary function of the participants according to their Locus of Symptom Limitation

	Breathlessness n=170	**Leg Discomfort n=521**	**Both n=219**	**General Fatigue n=46**	**Other n=269**	***P***
CanCOLD (%)	21/23/27/29	24/31/28/17[1]	18/35/24/23	32/24/22/22	23/31/28/18[1]	**0.043**
GOLD (0-4) (%)	45/26/22/7/0	55/28/15/2/0[1]	53/24/19/3/1	56/22/22/0/0	54/28/17/1/0	**0.014**
FVC, L	3.43[2.63-4.26]	3.66[2.99-4.45]	3.59[2.70-4.35]	3.62[2.84-4.27]	3.92[3.05-4.63][1]	**0.01**
FVC, %pred	99[88-112]	102[92-114]	100[89-112]	99[88-113]	105[92-115][1]	**0.02**
FEV_1, L	2.28[1.84-2.86]	2.59[2.07-3.18][1]	2.51[1.94-3.08]	2.62[2.0-2.97]	2.61[2.13-3.30][1]	**<0.001**
FEV_1, %pred	89[75-101]	95[82-105][1]	90[78-102]	90[79-104]	97[81-106][1,3]	**<0.001**
FEV_1/FVC, %	69[61-76]	71[64-78]	71[63-77]	72[64-75]	71[65-77]	0.182
TLC, L	5.94 [5.12-7.30]	6.18 [5.31-7.07]	6.23 [5.16-7.30]	6.21 [5.26-7.31]	6.55 [5.27-7.65]	0.086
TLC, %pred	107[94-116]	105 [95-115]	105[96-117]	109[96-117]	108[97-116]	0.295
RV, L	2.51[1.97-3.07]	2.36[1.9-2.86]	2.46[2.02-2.90]	2.48[1.99-3]	2.44[1.99-2.88]	0.192
RV%pred	114[90-139]	108 [89-128]	110[91-139]	112[97-138]	110[94-128]	0.076
RV%TLC	40[35-47]	38[33-45]	40[34-47]	40[35-45]	38[32-45][1]	**0.009**
FRC, L	3.39[2.80-4.16]	3.36[2.75-3.92]	3.40[2.85-3.98]	3.48[2.93-4.09]	3.44[2.99-4.19]	0.105
FRC%pred	108[92-127]	103[89-122]	108[89-128]	113[100-126]	108[93-124]	**0.029***
IC, L	2.66[2.12-3.26]	2.86[2.24-3.41]	2.74[2.08-3.40]	2.72[2.25-3.36]	2.87[2.33-3.57]	0.095
IC, % pred	101 [91-113]	103 [89-119]	102 [89-116]	105 [91-116]	105 [91-117]	0.63
DLCO, ml/min/mmHg	20[15-25]	20[16-25]	21[16-26]	22[15-25]	21[17-28]	0.22
DLCO, %pred	98[81-118]	99[84-118]	100[81-123]	106[89-121]	105[88-130]	**0.044***
DLCO/VA, ml/min/mmHg/L	4.02[3.46-4.60]	3.91[3.44-4.50]	3.97[3.46-4.47]	3.78[3.24-4.50]	3.98[3.46-4.55]	0.788
DLCO/VA, %pred	110[93-121]	105[93-117]	104[93-119]	104[89-119]	108[93-119]	0.451
Raw, cmH2O/L/sec	2.29[1.73-3.17]	2.12[1.67-2.88]	2.08[1.60-2.79]	2.20[1.60-3.13]	1.90[1.46-2.97]	0.11
Raw, %pred	66[48-90]	61[47-81]	59[46-79]	62[45-88]	53[41-83]	0.052

1 Statistical difference with breathlessness; 3 Statistical difference with both, * without difference in pairwise comparison.

Legend: COPD: Chronic Obstructive Pulmonary Disease; FVC: forced vital capacity; FEV_1: forced expiratory volume in the first second; TLC: total lung capacity; RV: residual volume; FRC: functional residual capacity; IC: inspiratory capacity; DLCO: diffusing capacity for carbon monoxide; Raw: airway resistance.

Table 2. Participants demographic characteristics according to their Locus of Symptom Limitation

	Breathlessness n=170	**Leg Discomfort n=521**	**Both n=219**	**General Fatigue n=46**	**Other n=269**	***P***
Sex, male/female %	55/45	57/43	53/47	57/43	63/37	0.269
Age, yrs	67 [61-74]	66 [59-73]	65 [60-72]	67 [57-73]	67 [60-75]	0.349
Height, cm	167 [160-175]	169 [162-175]	167 [161-175]	166 [161-174]	171 [163-177]	0.055
Weight, Kg	79 [67-88]	78 [66-88]	76 [67-88]	76 [67-84]	77 [66-88]	0.720
BMI, Kg/m^2	28 [24-30]	27 [24-30]	27 [24-30]	27 [24-29]	27 [24-29]	0.062
Race, %Caucasian	96	95	95	94	94	0.392
Cigarette status, never/ex-smokers/current, %	40/49/11	39/45/16	39/45/16	41/46/13	50/39/11	0.069
Pack years, yrs	6[0-33]	9[0-31][5]	7[0-31]	11[0-36][5]	0[0-22]	0.019
Comorbidities, yes n(%)						
Previous diagnosis of COPD	40(24%)	83(16%)	40(18%)	7(15%)	44(16%)	0.225
Previous diagnosis of Asthma	37(22%)	117(22%)	62(28%)	12(26%)	58(22%)	0.385
Pneumonia	38(22%)	97(19%)	34(16%)	11(24%)	48(18%)	0.419
Any musculoskeletal disease	79(46%)	261(50%)	103(32%)	19(63%)	122(45%)	0.202
Any cardiovascular disease (CVD)	96(56%)	251(48%)	105(48%)	18(39%)	123(46%)	0.146
CVD, excluding hypertension	53(31%)	154(30%)	51(23%)	11(24%)	62(23%)	0.130
Diabetes	14(8%)	49(9%)	23(11%)	2(4%)	27(10%)	0.719
Exacerbation and hospitalization, yes n(%)						
COPD exacerbation with use of antibiotics	8(5%)	16(3%)	8(4%)	2(4%)	8(3%)	0.852
COPD exacerbation with use of prednisone	5(3%)	5(1%)	5(2%)	0(0%)	4(2%)	0.304
COPD exacerbation with visit at the ER	2(2%)	2(1%)	3(2%)	1(1%)	2(1%)	0.498
COPD exacerbation with a hospitalization	1(1%)	1(1%)	1(1%)	0(0%)	2(1%)	0.794
Any respiratory medication	46(27%)	114(22%)	40(26%)	8(13%)	45(22%)	0.248
Heath status and symptom burden						
MRC, 1-5 pts	1.0[1.0-2.0][5]	1.0[1.0-2.0][5]	1.0[1.0-2.0][5]	1.0[1.0-2.0][5]	1.0[1.0-1.7]	**<0.001**
CAT, 0-40 pts	6.0[3.0-11.0][5]	5.0[3.0-9.0]	6.0[3.0-10.0]	5.0[3.0-8.0]	4.0[2.0-8.0]	**0.013**
Mental Component SF36, 0-100 pts	53[48-57]	53[47-56]	53[48-56]	52[46-57]	53[47-57]	0.910
Physical Component SF36, 0-100 pts	52[47-57][5]	53[46-57][5]	53[47-57][5]	54[48-58]	55[49-58]	**0.007**
HADS-A, 0-21 pts	3[2-6]	3[1-5]	4[2-6]	3[2-7]	3[2-5]	0.259
HADS-D, 0-21 pts	2[1-4]	2[1-4]	2[1-4]	2[1-3]	2[1-4]	0.271
CHAMPS, activities ≥ 3 METs, hrs/wk	1.95[0.56-3.75]	1.58[0.55-3.06]	1.88[0.47-3.59]	1.38[0.51-2.52][1]	2.11[0.75-4.07]	**0.035**
CHAMPS all activities, hrs/wk	3.78[2.14-5.77]	3.37[1.88-5.27]	3.73[2.12-5.86]	2.64[1.86-3.45][1,3,5]	3.79[2.10-6.09]	**0.006**

1 Statistical difference with breathlessness; 3 Statistical differences with both and 5 Statistical difference with other.

Legend: BMI: Body mass index; COPD: Chronic Obstructive Pulmonary Disease; MRC: medical research council dyspnea scale; CAT: COPD assessment test; SF36: short form-36 version; HADS: Hospital anxiety and depression scale; CHAMPS: Community Healthy Activities Model Program for Seniors.

Exercise responses

1. Physiology

The median (IQR) (unadjusted) of physiological and perceptual responses to CPET according to LOSL are presented in Table 3. Figures 3-4 and Supplementary Table E1 present the results of the between group adjusted analyses. Supplementary Table E4-5 shows the results of diagnose-based analysis. After adjusting for participant age, sex, height, body mass, cigarette pack-years, FEV_1(L) and RV(%TLC), the 'breathlessness' LOSL group had a significantly higher PPO and peak V'_E compared to the 'leg discomfort' and 'other' groups (PPO: 121 *vs* 107 and 112 watts; V'_E: 63 vs 58 and 56 L/min, respectively), and a significantly higher $V'O_{2\ peak}$ and peak HR, compared to the 'leg discomfort' group ($V'O_{2\ peak}$: 1.76 *vs* 1.63 L/min and HR: 139 *vs* 133 beats/min, respectively) (Table 3, Figure 3 and Supplementary Table E1).

In the adjusted analyses, there were no between group differences for gas exchange, as assessed with $V'_E/V'CO_2$ (slope or nadir) or SpO_2 (Figure 4 and Supplementary Table E2). The 'breathlessness' group, however, have evidence of greater inspiratory constraints on tidal volume expansion at end exercise and dynamic hyperinflation, particularly compared to the 'leg discomfort' and 'both' LOSL groups (Figure 4, Table E4). The 'breathlessness' group had a lower IRV at end exercise compared to the 'leg discomfort' and 'both' groups, a greater change in IC from rest to peak exercise compared to the 'leg discomfort' group, and a lower IC at end exercise compared to 'both' group. The greater ventilatory limitations in the 'breathlessness' group were also reflected in the higher proportion of people reaching previously defined critical values for breathing reserve (i.e. V'_E%MVV), tidal

volume constraints (i.e. V_T%IC, and IRV ≤70ml) and dynamic hyperinflation (ΔIC) (Table 3, Figure 5 and Supplementary Table E2).

2. Symptoms

As expected, participants in the 'breathlessness' group had higher Borg breathlessness intensity ratings at end exercise (absolute and relative to any given V'_E) compared to participants in the groups 'leg discomfort' and 'other' (Figure 4). Similarly, the 'breathlessness' group had lower Borg ratings of leg discomfort (absolute and relative to any given level of $V'O_2$) at end exercise compared to the 'leg discomfort' and 'general fatigue' groups (Table 3, Figure 4 and Supplementary Table E3). Not all participants who stopped the exercise due to breathlessness reported a higher Borg dyspnea rate than leg discomfort. Of those, 32% (n=55) reported leg discomfort greater than or equal to dyspnea (both assessed by Borg ratings).

Diagnosis-based results

People without COPD who stop exercise due to breathlessness present higher values of exercise capacity. More than a half are classified above the thresholds for ventilatory inefficiency, breathing reserve and inspiratory constrains, supporting the previous results (Supplementary Table E4). Regarding the differences between those with COPD diagnosis or not, the majority of differences is between people without COPD *vs* people with moderate-very severe COPD. Never smokers without COPD present similar values of dyspnea according to the BORG scale and lower values of leg discomfort complain than other groups (Supplementary Table E5). This can imply that these participants have good muscle capacity which allows them to achieve higher values of VO_2, despite their present lung alteration that can lead to worse impact along the years.

Table 3. Exercise physiological and perceptual responses according to the Locus of Symptom Limitation

	Breathlessness n=170	**Leg Discomfort n=521**	**Both n=219**	**General Fatigue n=46**	**Other n=269**	***P***
Exercise capacity						
Peak Power Output, watts	100 [80-140]	100 [80-140]	100 [80-140]	110 [80-140]	110 [80-150]	0.524
Peak Power Output, %pred	89 [73-105]	83 [68-99]	87 [69-105]	89 [73-109]	85 [69-108]	**0.036***
Cardiometabolic responses						
O_2 Pulse, mL O_2/heart beat	12 [9-14]	12 [9-15]	12 [9-15]	12 [9-14]	12 [10-15]	0.481
HR, beats/min	135 [119-155]	135 [118-150]	141 [122-156]	138 [117-153]	141 [118-156]	**0.047***
HR, %pred	94 [82-103]	93 [80-101]	95 [84-105]	94 [84-100]	95 [85-106][2]	**0.022**
Mean arterial pressure, mmHg	119 [109-126]	114 [105-123][1]	115 [107-125]	110 [101-124][1]	117 [107-126]	**0.004**
Symptom responses						
Dyspnea sensation, Borg 0-10	7[5-9]	5[3-7][1]	6[4-8][2,5]	6[4-8][2,5]	4[3-7][1,]	**<0.001**
Dyspnea/V'_E, Borg/(L/min)	0.11[0.08-0.16]	0.08[0.06-0.11][1]	0.10[0.04-0.13][2,5]	0.10[0.07-0.14][2,5]	0.07[0.052-0.11][1]	**<0.001**
Leg Discomfort, Borg 0-10	5[4-7]	7[5-9][1,5]	7[4-9][1,5]	7[5-9][1]	5[3-9]	**<0.001**
Leg Discomfort/$V'O_2$	3.33[2.25-4.84]	4.09[2.94-5.56][1,5]	3.85[2.88-5.39][1,5]	3.95[2.90-5.48][5]	3[1.86-4.77]	**<0.001**
Leg Discomfort/PPO	0.05[0.03-0.07]	0.06[0.04-0.08][1,5]	0.06[0.04-0.08][5]	0.06[0.04-0.08]	0.05[0.03-0.08]	**<0.001**
Gas Exchange parameters						
Respiratory exchange ratio	1.09 [1.03-1.15]	1.11 [1.04-1.16]	1.10 [1.04-1.16]	1.11 [1.05-1.20]	1.08 [1.01-1.14][1]	**0.001**
$V'O_2$, ml/kg/min	20 [16-26]	20 [17-25]	21 [16-27]	21 [16-25]	21 [16-28]	0.141
$V'O_2$, L/min	1.56 [1.16-2.06]	1.57 [1.18-2.04]	1.56 [1.20-2.09]	1.60 [1.17-1.99]	1.64 [1.24-2.20]	0.38
$V'O_2$, % pred	88 [76-102]	86 [72-100]	86 [72-104]	85 [72-106]	91 [73-110]	**0.09**
$V'CO_{2,\ L/min}$	1.79[1.26-2.32]	1.77[1.30-2.30]	1.73[1.25-2.29]	1.82[1.34-2.29]	1.79[1.31-2.42]	0.812
$V'_E/V'CO_2$	31[29-35]	32[29-35]	33[30-37][1,2,5]	32[28-35]	31[27-35]	**<0.001**
$V'_E/V'CO_2$ nadir	30[28-34]	30[28-33][5]	31[28-34][5]	30[27-34]	29[26-33]	**0.001**
$V'_E/V'CO_2$ ≥34, n(%)	48(28%)	131(25%)	74(34%)	13(28%)	63(23%)	0.085
$P_{ET}CO_2$, mmHg	37[33-39]	36[33-39]	36[33-39]	36[34-39]	37[33-40]	0.558
$P_{ET}CO_2$/ (V'E/$V'CO_2$ nadir)	39[36-42]	39[36-42]	39[36-42]	39[37-42]	39[36-43]	0.745
SpO_2, %	97[95-98]	97[96-98][1]	97[95-98]	97[96-98]	97[95-98]	**0.012**

Ventilatory parameters						
Respiratory Rate, breath/min	33 [29-38]	32 [27-36]	32 [27-37]	32 [27-38]	31 [26-35][1]	**0.033**
V'_E, L/min	56[40-73]	57[42-71]	59[43-78]	53[42-73]	53[41-73]	0.551
V'_E%MVV	72[57-88]	63[53-76][2,5]	69[58-85][5]	69[83-84]	61[48-78][1]	**<0.001**
V'_E%MVV ≥ 85, n (%)	56(33%)	68(13%)[1]	55(25%)[2]	11(24%)[2]	51(19%)[1]	**<0.001**
Vt, L	1.71[1.33-2.20]	1.82[1.42-2.31]	1.83[1.38-2.40]	1.74[1.50-2.25]	1.88[1.44-2.42]	0.225
V_T%IC	73[65-81]	68[60-76][1]	70[62-77]	66[60-75][1]	71[62-78][1]	**<0.001**
V_T%IC ≥73, n(%)	85(52%)	170(35%)[1]	88(42%)	16(37%)[1]	122(48%)	**<0.001**
IC, L	2.42[1.97-2.96]	2.71[2.20-3.23][1]	2.71[2.05-3.30][1]	2.68[2.35-3.08]	2.72[2.15-3.42][1]	**0.001**
ΔIC from rest, L	-0.18[-0.45-0]	-0.03[-0.32-0.20][1]	-0.13[-0.35-0.17][1]	-0.08[-0.32-0.27]	-0.06[-0.30-0.19]	**<0.001**
ΔIC ≥ 150ml, n(%)	90(56%)	186(39%)[1]	100(48%)	18(42%)	109(43%)	**0.004**
IRV, L	0.63[0.42-0.89]	0.86[0.59-1.14][1]	0.77[0.57-1.05][1]	0.93[0.61-1.17][1]	0.76[0.52-1.11][1]	**<0.001**
IRV≤ 70, n(%)	92(57%)	169(40%)[1]	83(40%)[1]	13(30%)[1]	110(43%)[1]	**<0.001**

*Without pairwise difference, 1 statistical difference with breathlessness, 2 statistical difference with leg discomfort, 5 statistical difference with other. HR: heart rate; V'_E: minute ventilation; $V'O_2$: Oxygen uptake; $V'CO_2$: carbon dioxide production; V_T: tidal volume; IC: inspiratory capacity; IRV: inspiratory reserve volume.

Supplementary Table E1. Adjusted comparison of exercise tolerance between Breathlessness vs the others LOSL groups.

	Adjusted mean	Breathlessness		
		Mean difference (95% CI)	Std. Error	*P*
Peak Power Output, watts				
Breathlessness	120.97	-	-	-
Leg Discomfort	107.33	13.64 (6.40, 20.89)	2.58	**<0.001**
Both	113.83	7.15 (-1.22, 15.51)	2.98	0.16
General Fatigue	115.02	5.96 (-7.39, 19.31)	4.75	1
Other	111.64	9.33 (1.26, 17.40)	2.87	**0.012**
$V'O_2$, L/min				
Breathlessness	1.76	-	-	-
Leg Discomfort	1.63	0.13 (0.02, 0.23)	0.04	**0.009**
Both	1.68	0.08 (-0.04, 0.21)	0.04	0.6
General Fatigue	1.67	0.09 (-0.11, 0.29)	0.07	1
Other	1.70	0.06 (-0.06, 0.18)	0.04	1
O_2 Pulse, mL O_2/beat				
Breathlessness	12.65	-	-	-
Leg Discomfort	12.30	0.35 (-0.35, 1.06)	0.25	1
Both	12.25	0.40 (-0.42, 1.22)	0.29	1
General Fatigue	12.43	0.22 (-1.09, 1.53)	0.47	1
Other	12.39	0.25 (-0.53, 1.04)	0.28	1
HR, beats/min				
Breathlessness	139.03	-	-	-
Leg Discomfort	132.78	6.25 (0.89, 11.61)	1.91	**0.01**
Both	136.65	2.38 (-3.83, 8.60)	2.21	1
General Fatigue	133.13	5.90 (-3.91, 15.71)	3.49	0.91
Other	135.59	3.44 (-2.53, 9.41)	2.12	1
Mean arterial pressure, mmHg				
Breathlessness	118.01	-	-	-
Leg Discomfort	114.04	3.97 (0.41, 7.53)	1.27	**0.02**
Both	115.15	2.87 (-1.23, 6.96)	1.46	0.49
General Fatigue	111.53	6.49 (-0.01, 12.99)	2.31	0.05
Other	116.70	1.32 (-2.68, 5.31)	1.42	1

Analyses were adjusted for: Age, Sex, Height, Weight, pack-years, FEV_1 (L) and RV%TLC.

Supplementary Table E2. Adjusted comparison of gas exchange and respiratory parameters after CPET between Breathlessness vs the other LOSL groups.

	Adjusted mean	Breathlessness		
		Mean difference (95% CI)	Std. Error	P
Respiratory exchange ratio				
Breathlessness	1.10	-	-	-
Leg Discomfort	1.10	-0.001 (-0.03, 0.03)	0.009	1
Both	1.10	0.0005 (-0.03, 0.03)	0.01	1
General Fatigue	1.12	-0.02 (-0.07, 0.03)	0.02	1
Other	1.07	0.03 (0.001, 0.06)	0.01	**0.039**
$V'CO_2$, L/min				
Breathlessness	1.94	-	-	-
Leg Discomfort	1.80	0.13 (0.01, 0.26)	0.043	**0.02**
Both	1.85	0.09 (-0.05, 0.23)	0.05	0.67
General Fatigue	1.88	0.06 (-0.17, 0.28)	0.08	1
Other	1.83	0.11 (-0.02, 0.25)	0.05	0.22
$V'_E/V'CO_2$				
Breathlessness	32.46	-	-	-
Leg Discomfort	32.88	-0.41 (-1.92, 1.10)	0.54	1
Both	34.76	-2.30 (-4.05, -0.55)	0.62	**0.002**
General Fatigue	31.84	0.62 (-2.18, 3.42)	0.99	1
Other	31.70	0.77 (-0.92, 2.45)	0.6	1
$V'_E/V'CO_2$ nadir				
Breathlessness	30.39	-	-	-
Leg Discomfort	31.17	-0.78 (-2.14, 0.58)	0.48	1
Both	31.96	-1.57(-3.15, -0.003)	0.56	0.049
General Fatigue	29.92	0.47 (-2.04, 2.98)	0.89	1
Other	29.95	0.44 (-1.08, 1.96)	0.54	1
$P_{ET}CO_2$, mmHg				
Breathlessness	35.72	-	-	-
Leg Discomfort	35.96	-0.23 (-1.48, 1.02)	0.44	1
Both	35.60	0.13 (-1.32, 1.57)	0.52	1
General Fatigue	35.69	0.04 (-2.34, 2.42)	0.85	1
Other	36.44	-0.71 (-2.10, 0.68)	0.5	1
$P_{ET}CO_2$/ ($V'_E/V'CO_2$ nadir)				
Breathlessness	38.79	-	-	-
Leg Discomfort	38.59	0.21 (-1.03, 1.44)	0.44	1
Both	38.67	0.13 (-1.30, 1.56)	0.51	1
General Fatigue	38.77	0.02 (-2.33, 2.38)	0.84	1
Other	38.93	*-0.14 (-1.51, 1.24)	0.49	1
SpO_2, %				
Breathlessness	95.87	-	-	-
Leg Discomfort	96.46	-0.59 (-1.26, 0.08)	0.24	0.14
Both	96.29	-0.43 (-1.20, 0.35)	0.28	1
General Fatigue	96.82	-0.95 (-2.19, 0.28)	0.44	0.3
Other	94.50	-0.63 (-1.38, 0.12)	0.27	0.19

Ventilatory parameters				
Respiratory Rate, breath/min				
Breathlessness	33.13	-	-	-
Leg Discomfort	32.02	1.11 (-0.73, 2.94)	0.65	0.9
Both	32.11	1.02 (-1.10, 3.14)	0.76	1
General Fatigue	32.56	0.57 (-2.84, 3.97)	1.21	1
Other	31.57	1.56 (-0.48, 3.61)	0.73	0.32
V'_E, L/min				
Breathlessness	62.56	-	-	-
Leg Discomfort	57.97	4.60 (-8.77, -0.42)	1.48	**0.02**
Both	62.63	-0.07(-4.89, 4.76)	1.72	1
General Fatigue	59.47	3.10 (-4.65, 10.84)	1.72	1
Other	56.30	6.26 (1.60, 10.91)	1.66	**0.002**
V_T, L				
Breathlessness	1.93	-	-	-
Leg Discomfort	1.86	0.07 (-0.02, 0.16)	0.03	0.22
Both	1.94	-0.01 (-0.11, 0.09)	0.04	1
General Fatigue	1.86	0.07 (-0.09, 0.24)	0.06	1
Other	1.86	0.07 (-0.03, 0.17)	0.04	0.41
V_T%IC				
Breathlessness	73.17	-	-	-
Leg Discomfort	67.84	5.33 (2.0, 8.65)	1.18	**<0.001**
Both	69.74	3.43 (-0.39, 7.25)	1.36	0.12
General Fatigue	66.02	7.15 (1.02, 13.27)	2.18	**0.01**
Other	69.76	3.41 (-0.28, 7.09)	1.31	0.09
IC, L				
Breathlessness	2.65	-	-	-
Leg Discomfort	2.74	-0.09 (-0.19, 0.005)	0.04	0.07
Both	2.79	-0.14 (-0.25, -0.02)	0.04	**0.007**
General Fatigue	2.79	-0.14 (-0.32, 0.04)	0.07	0.32
Other	2.70	-0.05 (-0.16, 0.06)	0.04	1
ΔIC from rest, L				
Breathlessness	-0.18	-	-	-
Leg Discomfort	-0.05	-0.13 (-0.23, -0.03)	0.04	**0.003**
Both	-0.08	-0.09 (-0.21, 0.02)	0.04	0.21
General Fatigue	-0.05	-0.13 (-0.31, 0.05)	0.07	0.43
Other	-0.10	-0.08 (-0.19, 0.03)	0.04	0.35
IRV, L				
Breathlessness	0.71	-	-	-
Leg Discomfort	0.89	-0.18 (-0.29, -0.07)	0.04	**<0.001**
Both	0.84	-0.13 (-0.26, -0.01)	0.04	**0.02**
General Fatigue	0.93	-0.09 (-0.28, 0.10)	0.07	1
Other	0.83	0.02 (-0.10, 0.13)	0.04	1

Analyses were adjusted for: Age, Sex, Height, Weight, pack-years, FEV_1 (L) and RV%TLC.

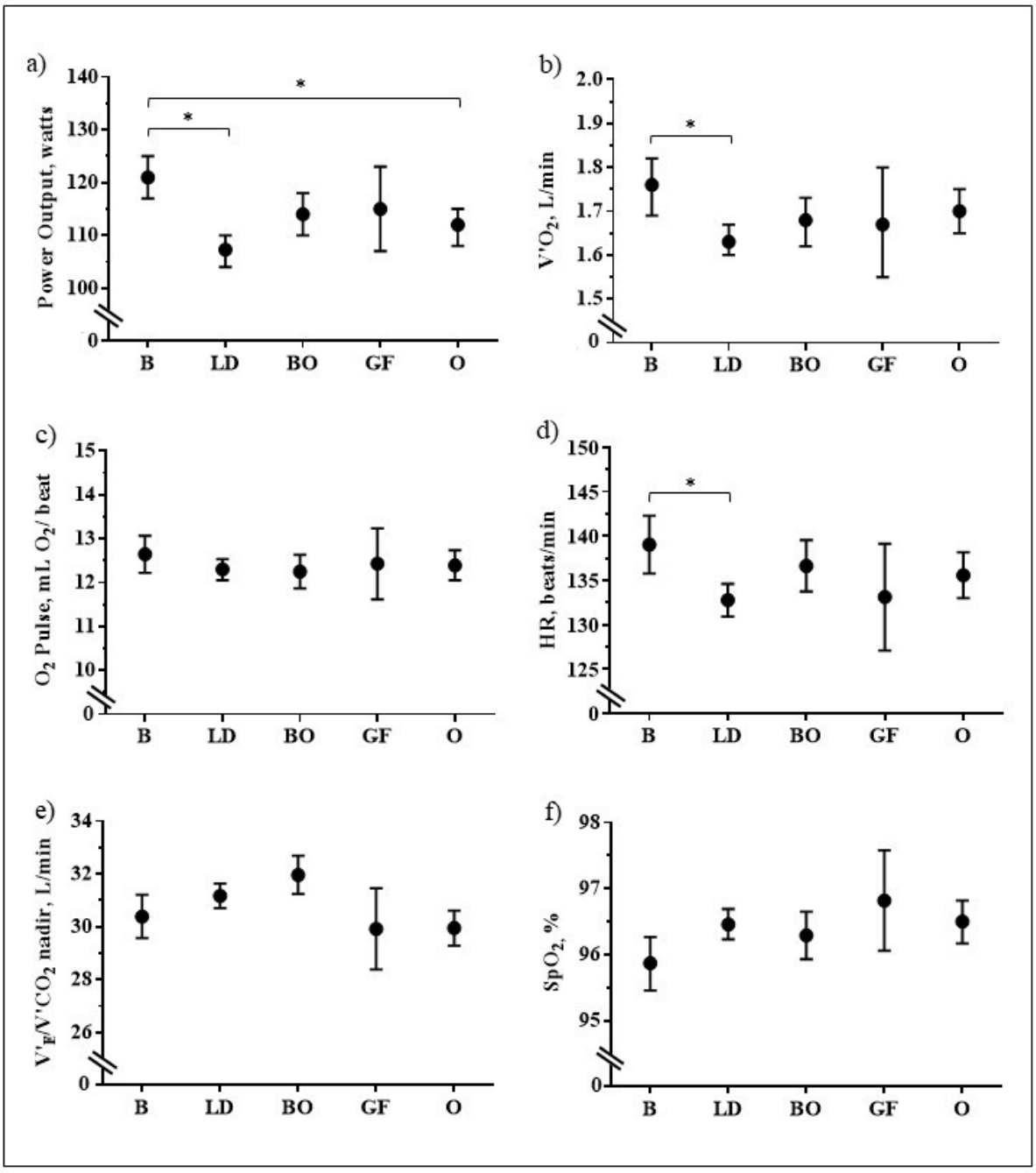


Figure 3. Differences in exercise tolerance between breathlessness vs other LOSL groups, after adjusted analysis.

Panel a) Peak Power Output; **Panel b)** peak $V'O_2$; **Panel c)** peak HR; **Panel d)** peak O_2 pulse; **Panel e)** V'_E/VCO_2 nadir and **Panel f)** SpO_2.

Data are expressed as adjusted mean (95%CI). * P ≤0.01

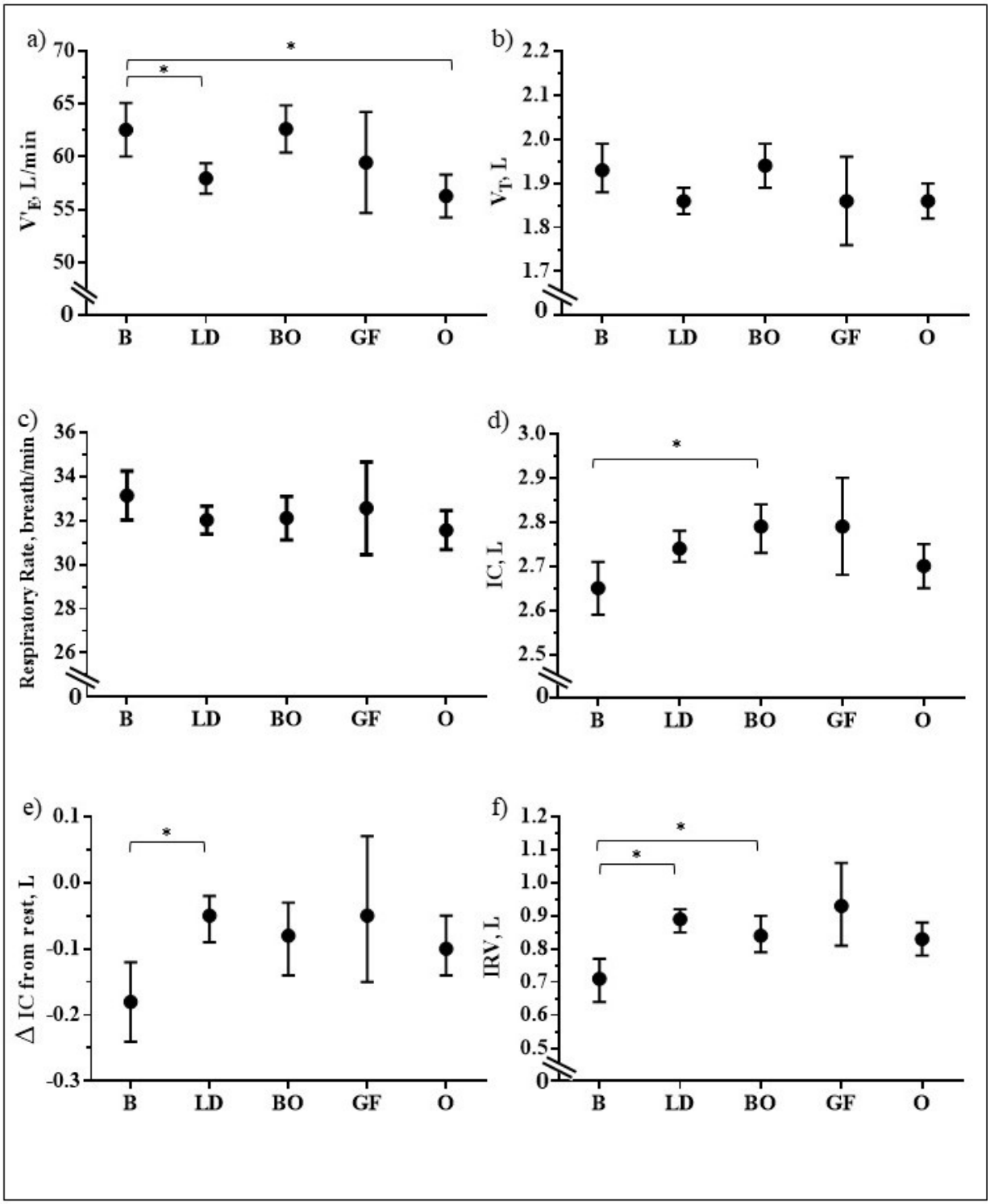


Figure 4. Adjusted comparison of ventilatory responses of the exercise between breathlessness and the other LOSL groups**. Panel a)** Ventilation (V'_E); **Panel b)** tidal volume (V_T); **Panel c)** respiratory rate; **Panel d)** inspiratory capacity (IC); **Panel e)** change in IC from rest (ΔIC) and **Panel f)** inspiratory reserve volume (IRV). Data are expressed as adjusted mean (95%CI). * P ≤0.007.

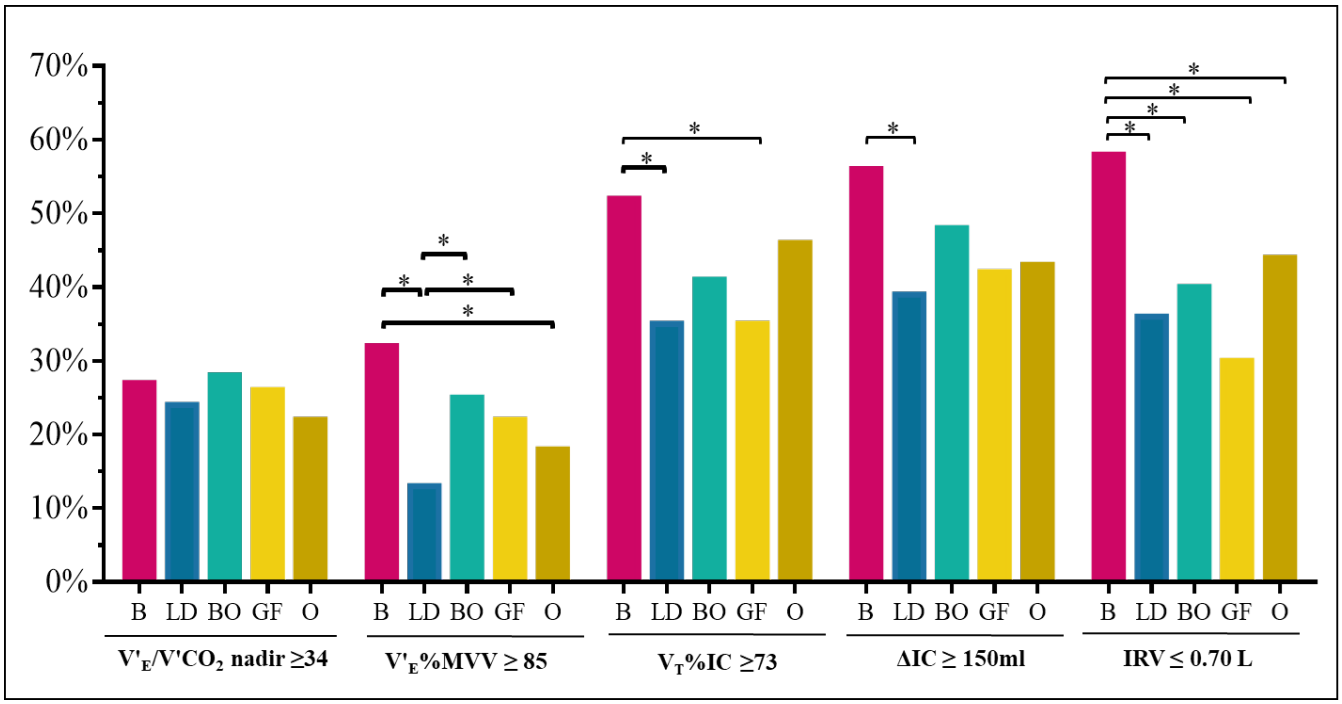


Figure 5. Comparison of the subject's proportion classified according to the thresholds for ventilatory inefficiency ($V'_E/V'CO_2$ nadir ≥34), breathing reserve (V'_E%MVV ≥85%); and inspiratory constrains (V_T%IC ≥ 73%; ΔIC from rest ≥150 ml and IRV ≤70ml) between the LOSL groups. * P <0.001.

Supplementary Table E3. Adjusted comparison of symptomatic exercise responses between Breathlessness vs the other LOSL groups.

	Adjusted mean	Breathlessness		
		Mean difference (95% CI)	Std. Error	P
Breathlessness, BORG 0-10				
Breathlessness	6.61	-	-	-
Leg Discomfort	4.80	1.81 (1.20, 2.43)	0.22	**<0.001**
Both	6.11	0.50 (-0.21, 1.21)	0.25	0.46
General Fatigue	6.06	0.53 (-0.60, 1.70)	0.41	1
Other	4.34	2.27 (1.59, 2.95)	0.24	**<0.001**
Breathlessness/V'_E				
Breathlessness	0.12	-	-	-
Leg Discomfort	0.09	0.03 (0.02, 0.05)	0.005	**<0.001**
Both	0.11	0.01 (-0.002, 0.03)	0.005	0.17
General Fatigue	0.11	0.008 (-0.02, 0.03)	0.009	1
Other	0.08	0.04 (0.02, 0.05)	0.005	**<0.001**
Leg Discomfort, BORG 0-10				
Breathlessness	5.43	-	-	-
Leg Discomfort	6.59	-1.17 (-1.80, -0.54)	0.22	**<0.001**
Both	6.34	-0.92 (-1.64, -0.19)	0.26	**0.004**
General Fatigue	6.51	-1.09 (-2.27, 0.10)	0.42	0.09
Other	5.50	-0.08 (-0.78, 0.63)	0.25	1
Leg Discomfort/$V'O_2$				
Breathlessness	3.53	-	-	-
Leg Discomfort	4.54	-1.01 (-1.56, -0.47)	0.19	**<0.001**
Both	4.33	-0.81 (-1.43, -0.18)	0.22	**0.003**
General Fatigue	4.44	-0.91 (-1.95, 0.12)	0.37	0.13
Other	3.64	-0.12 (-0.72, 0.49)	0.22	1
Leg Discomfort/PPO				
Breathlessness	0.053	-	-	-
Leg Discomfort	0.071	-0.02 (-0.03, -0.01)	0.003	**<0.001**
Both	0.063	-0.01 (-0.02, 0.0001)	0.004	0.05
General Fatigue	0.064	-0.01 (-0.3, 0.006)	0.006	0.61
Other	0.059	-0.006 (-0.02, 0.004)	0.004	0.78

Analyses were adjusted for: Age, Sex, Height, Weight, pack-years, FEV_1 (L) and RV%TLC.

Table E4. Exercise response comparison between LOSL groups according COPD diagnosis

Exercise capacity	Age		BMI		Peak Power Output, watts		Peak Power Output, %pred	
	No COPD	COPD	No COPD	COPD	No COPD	COPD	No COPD	COPD
Breathlessness	67[62-73]	67[61-77]	28[25-30]	28[24-30]	115[80-150]	100[70-140]	97[81-111][1]	83[69-94]
Leg discomfort	66[58-72]	66[60-74]	27[24-30]	27[24-30]	100[80-140]	100[80-130]	88[72-103][1,2,3,5]	76[63-92]
Both	65[60-72]	66[70-71]	27[25-31]	27[24-30]	110[80-150]	100[70-140]	93[78-110] [1,3,5]	78[66-98]
General Fatigue	64[55-68]	70[61-75]	27[23-29]	26[25-29]	115[100-140]	105[80-135]	87[74-110]	93[71-107]
Other	66[59-74]	68[62-75]	27[24-30]	26[23-29]	110[80-160]	100[70-130]	94[72-114] [1,3,5]	79[64-93]
P	0.19		0.67		**0.032**		**<0.0001**	

Cardiometabolic responses	$V'O_2$, ml/kg/min		$V'O_2$, L/min		Respiratory exchange ratio		O2 Pulse, mL O_2/heartbeat	
	No COPD	COPD	No COPD	COPD	No COPD	COPD	No COPD	COPD
Breathlessness	22[17-28]	19[15-25]	1.64[1.25-2.11]	1.48[1.15-1.93]	1.09[1.04-1.17]	1.08[1.03-1.14]	13[9-15]	12[10-14]
Leg discomfort	21[17-26]	19[17-24]	1.61[1.22-2.12] [5]	1.53[1.15-1.99]	1.11[1.06-1.17]	1.10[1.04-1.11]	12[9-15]	12[10-15]
Both	21[16-27]	21[15-26]	1.60[1.25-2.03]	1.53[1.15-2.12]	1.12[1.05-1.18]	1.08[1.03-1.16]	12[9-15]	11[9-15]
General Fatigue	21[15-26]	22[18-24]	1.60[1.18-2.08]	1.64[1.22-1.96]	1.11[1.06-1.22]	1.11[1.04-1.29]	12[9-15]	13[9-14]
Other	23[17-31]	21[16-27]	1.68[1.32-2.30]	1.63[1.21-1.99]	1.09[1.02-1.15][1,2]	1.06[1-1.3]	13[10-16]	12[9-15]
P	0.246		**<0.001**		**<0.001**		0.682	

Cardiometabolic responses	HR, beats/min		HR, %pred		Mean arterial pressure, mmHg		SpO_2, %	
	No COPD	COPD	No COPD	COPD	No COPD	COPD	No COPD	COPD
Breathlessness	141[124-158][1,2,3,5]	131[117-149]	98[86-106][1,2,3,5]	90[82-100]	118[108-129]	119[110-125]	97[96-98]	96[95-97]
Leg discomfort	138[122-154]	129[113-145]	95[86-102]	91[78-99]	115[107-123]	114[104-124]	97[96-99]	97[95-98]
Both	142[127-158]	141[121-155]	96[87-107]	94[82-103]	115[108-126]	115[107-124]	97[96-98]	96[95-97]
General Fatigue	141[113-154]	136[120-149]	95[74-100]	91[85-102]	109[101-124]	114[105-122]	98[97-98]	97[95-98]
Other	145[120-160]	136[116-153]	97[87-106]	94[84-105]	117[107-126]	117[107-125]	97[96-98]	97[95-98]
P	**<0.001**		**<0.001**		0.071		**<0.001**	

Symptom and gas exchange responses	Dyspnea sensation, BORG 0-10		Leg Discomfort, BORG 0-10		$VCO_{2,\ L/min}$		VE/VCO_2 nadir	
	No COPD	COPD	No COPD	COPD	No COPD	COPD	No COPD	COPD
Breathlessness	7[4-8] [1,2,3,5]	7[5-9]	7[4-8]	6[5-7]	1.91[1.38-2.40][2,4]	1.63[1.21-2.20]	29[27-32]	31[28-35]
Leg discomfort	5[3-7] [1,3]	4[3-7]	7[5-9] [1]	7[5-9]	1.84[1.32-2.34][2]	1.68[1.25-2.14]	29[27-32]	31[28-35]
Both	7[4-9] [5]	5[4-7]	7[4-9] [1]	6[4-8]	1.80[1.31-2.25] [5]	1.60[1.19-2.29]	30[28-33]	32[29-36]
General Fatigue	6[5-9]	6[5-8]	6[5-9]	7[5-8]	1.82[1.29-2.35]	1.82[1.47-2.07]	28[26-31]	31[28-34]
Other	4[3-7] [1,3,4]	4[3-6]	4[3-7] [2,3]	5[3-8]	1.82[1.39-2.61][2]	1.73[1.26-2.21]	28[26-32]	30[26-34]
P	**<0.001**		**<0.001**		0.161		**<0.001**	
Ventilatory parameters	**VE/VCO_2 ≥34**		**$P_{ET}CO_2$, mmHg**		**$P_{ET}CO_2$/ (V_E/VCO_2 nadir)**		**V_E, L/min**	
	No COPD	COPD	No COPD	COPD	No COPD	COPD	No COPD	COPD
Breathlessness	14 (18)	32 (34)	36[33-39]	38[34-41]	39[36-42]	39[36-43]	57[42-74]	54[39-73]
Leg discomfort	51 (18)	72 (31)	36[33-39]	36[34-39]	39[36-42]	38[35-42]	58[42-74]	55[43-68]
Both	23 (20)	39 (39)	36[34-38]	36[33-39]	39[37-42]	38[35-41]	58[42-74]	59[39-75]
General Fatigue	5 (22)	7 (35)	36[33-38]	36[35-39]	39[36-43]	39[37-41]	52[40-72]	59[44-72]
Other	27 (19)	31 (25)	36[33-40]	37[33-37]	40[36-43]	39[36-42]	55[42-80]	53[40-77]
P	**<0.001**		0.431		0.25		0.339	
Ventilatory parameters	**V_E, %pred**		**V_E%MVV**		**V_E%MVV ≥ 85**		**V_T, L/min**	
	No COPD	COPD	No COPD	COPD	No COPD	COPD	No COPD	COPD
Breathlessness	99 [81-134] [2,3,5]	117[88-137]	67[54-83] [2,3]	78[59-91]	16 (21)	38 (41)	1.67[1.39-2.22]	1.75[1.24-2.19]
Leg discomfort	89[75-107] [2,5]	101[86-120]	60[50-72] [2,5]	67[57-80]	25 (9)	42(18)	1.84[1.47-2.31]	1.77[136-2.31]
Both	99[84-116] [2,5]	112[92-132]	66[56-77] [2,5]	75[61-89]	19 (16)	36 (36)	1.82[1.43-2.35]	1.83[1.35-2.45]
General Fatigue	89[71-105] [2,5]	123[95-136]	59[48-71] [2,5]	83[64-91]	2 (8)	8 (40)	1.74[1.52-2.12]	1.77[1.45-2.28]
Other	88[70-114]	96[75-125]	59[47-76]	64[51-84]	21 (15)	28 (23)	1.93[1.42-2.54]	1.83[1.50-2.31]
P	**<0.001**		**<0.001**		**<0.001**		0.481	

Ventilatory parameters	V_T, %pred		V_T%IC		V_T%IC ≥73		IC, L	
	No COPD	COPD	No COPD	COPD	No COPD	COPD	No COPD	COPD
Breathlessness	94[79-198]	87[71-101]	72[63-80] [2]	74[66-83]	36 (50)	83 (38)	2.43[2.07-2.87]	2.37[1.77-3.05]
Leg discomfort	94[80-108] [5]	87[74-103]	67[58-75]	69[62-77]	83 (32)	47 (53)	2.77[2.26-3.24]	2.62[2.12-3.20]
Both	95[82-108]	87[77-104]	69[62-76]	71[63-79]	44 (40)	41 (41)	2.83[2.21-3.35]	2.56[1.95-3.24]
General Fatigue	97[81-101]	89[79-104]	65[58-71]	71[64-79]	5 (22)	10 (50)	2.74[2.413.15]	2.49[2.05-3.01]
Other	97[83-108]	92[76-103]	71[63-78]	72[61-79]	61 (44)	57 (49)	2.74[2.17-3.47]	2.67[2.08-3.36]
P	**0.001**		**<0.001**		**0.002**		**0.001**	

Ventilatory parameters	**ΔIC ≥ 150ml**		**IRV, L**		**IRV≤ 70**	
	No COPD	COPD	No COPD	COPD	No COPD	COPD
Breathlessness	36 (50)	54 (60)	0.71[0.48-0.96]	0.58[0.39-0.83]	35 (49)	59 (66)
Leg discomfort	81 (31)	105 (49)	0.90[0.62-1.20]	0.81[0.53-1.11]	84 (32)	88 (40)
Both	43 (39)	57 (58)	0.84[0.66-1.06] [2]	0.71[0.50-1.02]	35 (32)	49 (50)
General Fatigue	9 (39)	9 (45)	0.99[0.85-1.22]	0.82[0.56-1.05]	4 (17)	9 (45)
Other	52 (37)	57 (49)	0.82[0.52-1.17]	0.73[0.50-1.08]	56 (40)	56 (48)
P	**<0.001**		**<0.001**		**<0.001**	

1: difference between breathlessness COPD; 2: difference between leg discomfort COPD; 3: difference between both COPD; 4: difference between general fatigue COPD; 5: difference between other COPD. HR: heart rate; V'_E: minute ventilation; $V'O_2$: Oxygen uptake; $V'CO_2$: carbon dioxide production; V_T: tidal volume; IC: inspiratory capacity; IRV: inspiratory reserve volume.

Table E5. Exercise physiological and perceptual responses of those who stopped because of breathlessness, according CanCOLD groups.

	NS no COPD (n=36)	ES no COPD (n=39)	GOLD 1 (n=45)	GOLD 2+ (n=50)	*P*
Exercise capacity and Cardiometabolic responses					
Peak Power Output, watts	115 [75-145]	120 [85-155]	100 [90-140]	90 [60-120]	**0.04**
Peak Power Output, %pred	95 [80-111]*	102 [82-110]*	87 [78-105]	77 [59-90]	**<0.001**
$V'O_2$, L/min	1.60 [1.15-2.07]	1.79 [1.34-2.28]	1.66 [1.32-1.98]	1.37 [1.04-1.78]	0.089
$V'O_2$, % pred	92 [79-104]	95 [86-110]*	84 [76-101]	83 [65-95]	**0.005**
O_2 Pulse, mL O_2/heart beat	12 [9-14]	13 [10-15]	12 [10-14]	11 [9-13]	0.152
HR, beats/min	141 [125-166]	139 [123-157]	135 [119-150]	125 [115-146]	0.1
HR, %pred	99 [86-108]	97 [85-103]	94 [85-101]	94 [84-100]	0.05
Mean arterial pressure, mmHg	119[109-126]	115 [106-128]	117 [108-125]	120 [111-125]	0.338
Symptom responses					
Dyspnea sensation, BORG 0-10	6 [4-7]	7 [4-9]	7 [5-9]	7 [5-9]	0.073
Dyspnea/V'_E, BORG/(L/min)	0.11 [0.07-0.16]*	0.10 [0.08-0.13]*	0.11 [0.08-0.43]	0.13 [0.10-0.22]	**0.009**
Leg Discomfort, BORG 0-10	4 [3-5]*†	5 [4-7]	6 [4-7]	6 [5-7]	**0.001**
Leg Discomfort/$V'O_2$	2.61 [1.52-3.72]*	3.08 [2.06-3.81]	3.33 [2.83-4.90]	3.68 [3.03-5.81]	**0.002**
Leg Discomfort/PPO	0.04 [0.02-0.06]*	0.05[0.03-0.06]*	0.05[0.04-0.07]	0.06 [0.04-0.10]	**0.001**
Gas Exchange parameters					
$V'CO_{2,\ L/min}$	1.89[1.21-2.31]	1.95[1.50-2.50]	1.80[1.38-2.50]	1.52[1.08-2.06]	0.048
$V'_E/V'CO_2$ nadir	29[27-32]	28[27-32]	31[28-35]	30[28-34]	0.095
$V'_E/V'CO_2$ ≥34, n(%)	6(18%)	7(19%)	13(31%)	19(40%)	0.078
$P_{ET}CO_2$, mmHg	36[34-39]*	35[32-38]*	35[31-39]*	39[36-42]	**<0.001**
$P_{ET}CO_2$/ ($V'_E/V'CO_2$ nadir)	39[37-42]	40[36-42]	38[33-41]*	41[38-43]	**0.028**
SpO_2, %	97[96-98]**	97[96-98]	96[95-97]	96[93-97]	**0.003**
Ventilatory parameters					
V'_E, L/min	56[41-68]	60[47-84]	60[46-87]*	50[35-65]	**0.026**
V'_E, %pred	94[74-116]*	101[84-125]*	96[84-120]*	127[108-140]	**<0.001**
V'_E%MVV	63[49-78]*	67[56-84]*	64[56-80]*	85[72-94]	**<0.001**

V'_E%MVV ≥ 85, n (%)	6(18%)*	8(22%)	11(26%)	27(57%)	**<0.001**
V_T, L	1.69[1.39-2.10]	1.63[1.42-2.31]	1.92[1.60-2.47]*	1.43[1.08-1.93]	**0.001**
V_T % pred	97[85-112]*	91[77-105]*	99[85-110]*	73[65-87]	**<0.001**
V_T%IC	75[64-81]	71[61-79]	73[65-80]	76[66-85]	0.296
V_T%IC ≥73, n(%)	17(52%)	17(46%)	23(55%)	25(53%)	0.876
IC, L	2.31[2.06-2.72]*	2.55[2.29-3.06]*	2.82[2.44-3.23]*	1.89[1.61-2.33]	0.344
IC, %pred	91[83-96]*	94[82-105]*	100[89-105]*	69[62-75]	**0.001**
ΔIC from rest, L	-0.07[-0.23-0.02]*	-0.18[-0.36-0.02]	-0.07[-0.47-0.16]*	-0.36[-0.55- -0.16]	**0.002**
ΔIC ≥ 150ml, n(%)	14(42%)	21(57%)	17(41%)*	36(77%)	**0.002**
IRV, L	0.66[0.42-0.89]	0.74[0.48-1.02]*	0.51[0.77-1.09]*	0.49[0.34-0.63]	**<0.001**
IRV≤ 70, n(%)	17(52%)*	16(43%)*	19(45%)*	41(87%)	**<0.001**

*Difference with GOLD2+; †statistical difference with GOLD1. HR: heart rate; V'_E: minute ventilation; $V'O_2$: Oxygen uptake; $V'CO_2$: carbon dioxide production; V_T: tidal volume; IC: inspiratory capacity; IRV: inspiratory reserve volume.

DISCUSSION

The present study is the first to report the distribution of reasons to stopping symptom-limited cardiopulmonary cycle exercise testing in a large population-based sample of Canadian adults aged ≥40 years with and without diagnosis of COPD. According to the results, leg discomfort alone or as a co-primary symptom is the most common reason to stop the exercise. Contrary to the initial hypothesis, the breathlessness group did not present worse sociodemographic characteristics, dyspnea during daily activities (MRC) or exercise capacity than the other LOSL groups. However, the results confirm, either after adjusted and unadjusted analysis, and diagnosis-based comparison, that breathlessness group had worse mechanical constraints than those who stop the exercise due to leg discomfort.

The distribution of LOSL prevalence found in the present study corroborates with was shown by most previous studies with health and symptomatic outpatient populations (5, 8, 9, 28). Studies that present controversial results and reported breathlessness as the major LOSL had sample with greater airflow obstruction than the present (10, 29). This is likely to explain the discrepancy, since Tracey et al. (8) showed that subjects with worse COPD are more likely to report breathlessness as their LOSL. Nonetheless, the present study showed that although the breathlessness group is composed by a higher proportion of participants with moderate-severe COPD, the major reason to stop the exercise in all CanCOLD groups was leg discomfort and this was independently of COPD diagnosis.

Despite the difference in pulmonary function, subjects who stopped the exercise due to breathlessness present better exercise tolerance when it was corrected by demographic characteristics and pulmonary function. This better exercise capacity could be associated to the nature of the test. Some studies

describe breathlessness complaint as the most common LOSL during tests based on walking activities, while leg discomfort as a primary or co-primary symptom is more likely reported in cycle tests (constant or incremental) (28,30). Additionally, during cycle tests, people who do not develop quadriceps fatigue after exercise are more likely to report breathlessness as their LOSL and have longer exercise time than those who stopped the exercise due to leg discomfort (6,7,31).

Although the breathlessness group had better exercise tolerance than the subjects who stopped because leg discomfort, they present more gas trapping and mechanical constraints than all the other groups, corroborating with the findings by Tracey et al. (8). More than half of the subjects in the breathlessness group were classified above the threshold of V_T%IC of ≥73%. It implies that these subjects have a severe dynamic restrictive constraint on V_T expansion (29). Also, they present higher dynamic hyperinflation, assessed by the decline in IC≥150ml. Despite the evidence of critical inspiratory constrains being greater in the breathlessness group, V'_E%MVV was not different between LOSL groups, which supports the previous findings that this index is a poor indicator of ventilatory limitation to exercise (including breathlessness) (32).

The restriction described above was previously related as an important factor that contributes to exercise intolerance in subjects with COPD (8,29). Interestingly, in the present study these restrictions were not related to presence of COPD diagnosis, and it remained even after the correction analysis. This increases the importance of performing the CPET as a way to identify the LOSL and tracking apparently healthy individuals, without limiting symptoms during daily life, but with pulmonary changes capable of having a great impact on daily life if not treated properly. Further, these changes can explain why these subjects respond better to bronchodilator therapy

with an increase in endurance time than the subjects who stop due to leg discomfort (6-8,28).

Similarly to the literature, the present results showed that Borg ratings are associated with the reason to stop the exercise reported by the subjects (28-30). However, it is important to emphasize that Borg ratings cannot replace the LOSL reported directly by the subject, since not all participants who report breathlessness as their LOSL had higher Borg dyspnea values at the end of exercise, and this is also true for those who report leg discomfort as their LOSL (8).

LIMITATIONS AND CLINICAL IMPLICATIONS

Despite the novel information and good clinical applicability, the present study had some limitations. First, the absence of objective measurement of quadriceps contractile fatigue or mass strength; and second, the absence of CEPT performed in treadmill what hinders the reproducibility of these results to subjects assessed in this way.

The present study may be clinically meaningful since it indicates that in the general population of older and mostly asymptomatic adults, resting lung function tests, as well as routine assessments of shortness of breath (mMRC) and symptom burden (CAT), fail to discriminate people with pathophysiological abnormalities in the behavior of dynamic operating lung volumes during exercise and breathlessness as a LOSL.

Furthermore, although exercise interruption due to breathlessness is relatively uncommon – occurring in 14% of our CanCOLD population, this group of people exhibits abnormalities in the behavior of dynamic operating lung volumes during exercise. This justifies future research on the response of this group of people to

early interventions with respiratory medications (inhalers), particularly about relieving exertion breathlessness and improving exercise tolerance. Also, a follow-up research would be useful to verify if participants in the present study who stopped exercising due to shortness of breath have worse long-term health outcomes (e.g., decline in lung function, exercise tolerance, exacerbations, worsening of health, etc.), since breathlessness as LOSL is known to foreshadow premature death (33, 34).

ACKNOWLEDGMENTS

The authors appreciate the assistance of Pei Zhi Li, without whom this study could not have been completed. Also, we would like to thank all the colleagues from Clinical Exercise and Respiratory Physiology Laboratory for their support and assistance and the subjects for agreeing to participate. Also, all members of the CanCOLD group, as below:

Members of the CanCOLD Collaborative Research Group:

Executive Committee: Jean Bourbeau (McGill University, Montreal, Canada); Wan C. Tan, J. Mark FitzGerald; Don Sin (UBC, Vancouver, Canada); Darcy Marciniuk (University of Saskatoon, Saskatoon, Canada) Dennis E. O'Donnell (Queen's University, Kingston, Canada); Paul Hernandez (Dalhousie University, Halifax, Canada); Kenneth R. Chapman (University of Toronto, Toronto, Canada); Robert Cowie (University of Calgary, Calgary, Canada); Shawn Aaron (University of Ottawa, Ottawa, Canada); F. Maltais (University of Laval, Quebec City, Canada); *International Advisory Board:* Jonathon Samet (Keck School of Medicine of USC, Los Angeles, CA); Milo Puhan (John Hopkins School of Public Health, Baltimore, MD); Qutayba Hamid (McGill University, Montreal, Canada); James C. Hogg (UBC James Hogg Research Center, Vancouver, Canada). *Operations Center:* Jean Bourbeau (PI), Carole Baglole, Carole

Jabet, Palmina Mancino, Yvan Fortier (University of McGill, Montreal, Canada); Wan C. Tan (co-PI), Don Sin, Sheena Tam, Jeremy Road, Joe Comeau, Adrian Png, Harvey Coxson, Miranda Kirby, Jonathon Leipsic, Cameron Hague (University of British Columbia James Hogg Research Center, Vancouver, Canada). *Economic Core:* Mohsen Sadatsafavi (University of British Columbia, Vancouver, Canada). *Public Health Core:* Teresa To, Andrea Gershon (University of Toronto, Toronto, Canada). *Data Management and Quality Control*: Wan C. Tan, Harvey Coxson (UBC, Vancouver, Canada); Jean Bourbeau, Pei-Zhi Li, Jean-Francois Duquette, Yvan Fortier, Andrea Benedetti, Denis Jensen (McGill University, Montreal, Canada); Denis O'Donnell (Queen's University, Kingston, Canada). *Field Centers:* Wan C. Tan (PI), Christine Lo, Sarah Cheng, Cindy Fung, Nancy Haynes, Junior Chuang, Licong Li, Selva Bayat, Amanda Wong, Zoe Alavi, Catherine Peng, Bin Zhao, Nathalie Scott-Hsiung, Tasha Nadirshaw (UBC James Hogg Research Center, Vancouver, Canada); Jean Bourbeau (PI), Palmina Mancino, David Latreille, Jacinthe Baril, Laura Labonte (McGill University, Montreal, Canada); Kenneth Chapman (PI), Patricia McClean, Nadeen Audisho (University of Toronto, Toronto, Canada); Robert Cowie (PI), Ann Cowie, Curtis Dumonceaux, Lisette Machado (University of Calgary, Calgary, Canada); Paul Hernandez (PI), Scott Fulton, Kristen Osterling (Dalhousie University, Halifax, Canada); Shawn Aaron (PI), Kathy Vandemheen, Gay Pratt, Amanda Bergeron (University of Ottawa, Ottawa, Canada); Denis O'Donnell (PI), Matthew McNeil, Kate Whelan (Queen's University, Kingston, Canada); Francois Maltais (PI), Cynthia Brouillard (University of Laval, Quebec City, Canada); Darcy Marciniuk (PI), Ron Clemens, Janet Baran (University of Saskatoon, Saskatoon, Canada).

REFERENCES

1. Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2021. Available at: www.goldcopd.org.
2. Neder, J.A., et al. Physiological and clinical relevance of exercise ventilatory efficiency in COPD. Eur Respir J, 2017; 49(3)
3. Oga, T., et al., Exercise capacity deterioration in patients with COPD: longitudinal evaluation over 5 years. Chest, 2005; 128(1):62-9.
4. Radtke, T, Crook, S, Kaltsakas, G, Louvaris, Z, Berton D, Urquhart, DS, et al. ERS statement on standardization of cardiopulmonary exercise testing in chronic lung diseases. Eur Respir J, 2019; 54: 1901441.
5. Killian, K.J., et al., Exercise capacity and ventilatory, circulatory, and symptom limitation in patients with chronic airflow limitation. Am Rev Respir Dis, 1992. 146(4): 935-40.
6. Saey, D., et al. Contractile leg fatigue after cycle exercise: a factor limiting exercise in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med, 2003; 168(4):425-30
7. Deschenes, D., et al. Locus of symptom limitation and exercise response to bronchodilation in chronic obstructive pulmonary disease. J Cardiopulm Rehabil Prev, 2008; 28(3): 208-14.
8. Tracey, L., et al. Physiological responses to exercise according to the locus of the symptom limitation in people with COPD. Respir Physiol Neurobiol, 2019; 273: 103322.
9. Hamilton, A.L., et al., Symptom intensity and subjective limitation to exercise in patients with cardiorespiratory disorders. Chest, 1996; 110(5): 1255-63.

10. O'Donnell, D.E., et al., Reliability of ventilatory parameters during cycle ergometry in multicentre trials in COPD. Eur Respir J, 2009; 34(4): 866-74.
11. Bourbeau J, Tan WC, Benedetti A, et al. Canadian Cohort Obstructive Lung Disease (CanCOLD): Fulfilling the need for longitudinal observational studies in COPD. COPD. 2014;11(2):125–132.
12. Bestall, JC, et al., Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. Thorax, 1999; 54(7): 581-6.
13. Stewart AL, Mills KM, King AC, Haskell WL, Gillis D, Ritter PL. CHAMPS physical activity questionnaire for older adults: outcomes for interventions. Med Sci Sports Exerc, 2001 Jul; 33(7):1126-41.
14. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care, 1992; Jun; 30(6):473-83.
15. Jones, PW, et al., Development and first validation of the COPD Assessment Test. Eur Respir J, 2009; 34(3): 648-54.
16. Zigmond AS, Snaith RP. Th e hospital anxiety and depression scale. Acta Psychiatr Scand, 1983; 67(6): 361–70.
17. American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. Th is official statement of the American Thoracic Society was adopted by the ATS Board of Directors, November 1986. Am Rev Respir Dis, 1987; 136(1):225–44;
18. Gandevia, B., & Hugh-Jones, P., Terminology for measurements of ventilatory capacity. Thorax, 1957; 12: 290-3.

19. Buist AS, Vollmer WM, Sullivan SD, Weiss KB, Lee TA, Menezes AM, et al. The Burden of Obstructive Lung Disease Initiative (BOLD): rationale and design. COPD, 2005; 2(2): 277–83.
20. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. Am J Respir Crit Care Med, 1999; 159:179–87.
21. ATS/ACCP. Statement on cardiopulmonary exercise testing. Am J Respir Crit Care Med, 2003; 167(2):211–77.
22. Borg, GA, Psychophysical bases of perceived exertion. Med Sci Sports Exerc, 1982; 14(5): 377-81
23. Lewthwaite, H., et al.. Normative peak cardiopulmonary exercise test responses in Canadian adults aged ≥40 years. Chest, 2020; 20-1412.
24. Neder, JA, Berton, DC, Marillier, M, Bernard, AC, O'Donnell, DE & on behalf of the Canadian Respiratory Research Network. Inspiratory constrains and ventilatory inefficiency are superior to breathing reserve in the assessment of exertional dyspnea in COPD. COPD, 2019; 16(2):174-81.
25. O'Donnell, DE, Guenette, JA, Maltais, F, Webb, KA. Decline of resting inspiratory capacity in COPD. Chest, 2012; 141(3):753-62.
26. Radtke, T, Crook, S, Kaltsakas, G, Louvaris, Z, Berton D, Urquhart, DS, et al. ERS statement on standardisation of cardiopulmonary exercise testing in chronic lung diseases. Eur Respir J, 2019; 54: 1901441.
27. Chin RC, Guenette JA, Cheng S, Raghavan N, Amornputtisathaporn N, Cortés-Tellés A, Webb KA, O'Donnell DE. Does the respiratory system limit exercise in mild chronic obstructive pulmonary disease? Am J Respir Crit Care Med,, 2013; 187:1315–23.

28. Maltais F, O'Donnell DE, Hamilton A, Zhao Y, Casaburi R. Comparative measurement properties of constant work rate cycling and the endurance shuttle walking test in COPD: the TORRACTO clinical trial. Ther Adv Respir Dis 2020; 14:1-11.
29. O'Donnell DE, Revill SM, Webb KA. Dynamic hyperinflation and exercise intolerance in chronic obstructive pulmonary disease. Am J Respir Crit Care Med, 2001; 164:770-77.
30. Man, W.D., et al., Symptoms and quadriceps fatigability after walking and cycling in chronic obstructive pulmonary disease. Am J Respir Crit Care Med, 2003; 168: 562-67.
31. Mador, M.J., et al., Contractile fatigue of the quadriceps muscle predicts improvement in exercise performance after pulmonary rehabilitation. J Cardiopulm Rehabil Prev, 2014; 34(1): 54-61.
32. Neder, J.A., et al., Clinical interpretation of cardiopulmonary exercise testing: current pitfalls and limitations. Physiol, 2021; 12:552000.
33. Bodegard, J., et al. Reason for terminating an exercise test provide independent prognostic information: 2014 apparently health men followed for 26 years. Eur Heart J, 2005; 26:1394-1401.
34. Argulian, E., et al. Meta-Analysis of prognostic implications of dyspnea versus chest pain in patients referred for stress testing. Am J Cardiol, 2014; 113 (3): 559-64.

4 ARTICLE 2

Title: A breath of fresh air: validity and reliability of a Portuguese version of the Multidimensional Dyspnea Profile for patients with COPD.

Published in Plos One – Qualis: A1, Impact Factor: 3.24
(Belo et al., PLoS One. 2019 Apr 30;14(4):e0215544)

Authors: Letícia F. Belo[1], Antenor Rodrigues[1,2], Ana Paula Vicentin[1], Thaís Paes[1], Larissa A. de Castro[1], Nidia A. Hernandes[1], Fabio Pitta[1*].

[1]Laboratory of Research in Respiratory Physiotherapy (LFIP), Department of Physiotherapy, Universidade Estadual de Londrina (UEL), Londrina, Paraná, Brazil.
[2] PhD fellow at the Department of Rehabilitation Sciences, Katholieke Universiteit Leuven, Leuven, Belgium

Conflict of interest

LFB, AR, APV, TP, LAC, NAH and FP have no conflict of interest to disclose.

Authors' contributions:

LFB and FP are responsible for the manuscript content, data collection and veracity of the data analysis. AR, APV and TP contributed substantially to the data collection and study design, manuscript preparation and review of manuscript. LAC and NAH contribute to Portuguese translation of the MDP, study design and review of manuscript.

***Corresponding Author:**
E-mail: fabiopitta@uol.com.br (FP)

Abstract

Aim: To provide a Portuguese version of Multidimensional Dyspnea Profile (MDP), investigating its validity and reliability in Brazilian patients with COPD. **Methods:** This was a cross-sectional study for translation and linguist validation of the Portuguese MDP version for patients with COPD. This process occurs according to the protocol of Mapi Research Trust, Lyon, France. Three scores of MDP were used to analysis, the immediate unpleasantness of dyspnea (A1); the "immediate perception domain" (S) (sum of A1 plus the sensory descriptors) and the "emotional response domain" (A2) (sum of the emotional descriptors). The questionnaires COPD assessment Test (CAT), Hospital Anxiety and Depression scale (HADS) and Medical Research Council scale (MRC) were used as anchors to investigate MDP's validity. Internal consistency was assessed with Cronbach's alpha. Test–retest reliability was assessed with intraclass correlation coefficient (ICC) and concurrent validity was assessed with Spearman correlation coefficients. **Results:** Thirty patients with moderate-severe COPD were studied for the validation analysis (43% male, 63±8years, body mass index [BMI] 27±6Kg/m^2, forced expiratory volume in the first second [FEV_1] 48±15%predicted, six-minute walking test [6MWT] 464±84m and 84±16%predicted), whereas 10 patients were excluded due to missing data from the reliability analysis, resulting in a sample of 20 subjects for this purpose (50% male, 62±8years, BMI 27±6Kg/m^2, FEV_1 48±15%predicted, 6MWT 452±93m and 82±19%predicted). Both samples were similar regarding general characteristics (*P*>0,05 for all variables) MDP presented strong correlations, i.e., ICC intra-rater: A1: 0.77 (0.48–0.90), S: 0.78 (0.52–0.91), and A2: 0.85 (0.66-0.94), with high internal consistency (Cronbach's α 0.86, 0.88 and 0.92 respectively); and ICC inter-rater: A1: 0.74 (0.46–0.89), S: 0.75 (0.48–0.89) and A2: 0.91 (0.78-0.96) with Cronbach's α 0.85, 0.86 and 0.95 respectively. **Conclusion:** The Portuguese version of the MDP is the first valid and reliable instrument to assess the multidimensional dyspnea for Portuguese-speaking patients with COPD.

Introduction

Dyspnea is a major disabling symptom reported by patients with chronic obstructive pulmonary disease (COPD), described as a subjective experience, derived from interactions among multiple physiological, psychosocial, and environmental factors [1]. Noteworthy, the majority of available instruments in Portuguese assesses dyspnea only in an one-dimensional approach [2,3]. Therefore, an instrument in Portuguese language which is able to assess and distinguish multiple aspects of dyspnea is necessary.

The multidimensional dyspnea profile (MDP) is an instrument indicated for this purpose [4-7]. It assesses immediate respiratory discomfort, qualities of breathlessness, and emotional responses [4,6]. It is already known that MDP is sensitive to detect changes in dyspnea sensation evoked by different physiologic stimulus [6]. However, a Portuguese version of this instrument is not yet available, hindering its use in Portuguese-speaking countries. Therefore, the aim of this study was to provide a Portuguese version of MDP, investigating its validity and reliability in Brazilian patients with COPD.

Material and methods

This was a cross-sectional study involving the translation and linguist validation of the MDP. The Portuguese version has been developed by three of the present researchers (LFB, LAC and NAH) in collaboration with Robert Banzett and Mapi Research Trust, Lyon, France (https://eprovide.mapi-trust.org, contact for permission), according to standard process of forward and backward translations, followed by cognitive interviews with five patients with chronic respiratory disease (COPD, bronchiectasis and asthma) (S1 and S2 Appendix). The process was

undertaken similarly to the French version [7], and it was not necessary to adapt or withdraw any item of the instrument. Furthermore, patients with COPD (diagnosed according to international criteria) [8] were included, in whom the MDP was applied in three different time-points: day one and day two 24 hours apart, by different raters, and day three, by the first rater, one to two weeks after the first evaluation. The focus period was established as breathlessness during activities of daily living (ADL) on the past 2 weeks. Inclusion criteria were: one-month clinical stability and absence of severe and/or unstable cardiac disease and musculoskeletal comorbidities that could interfere in the assessments. Exclusion criteria were the occurrence of osteoneuromuscular complications or acute exacerbation during the assessment period. Patients missing any MDP assessment were excluded from the reliability analysis. The study was approved by the University's ethics committee (number: 1.887.424) and all patients provided informed consent.

The MDP consists of 11 items evaluating sensory and affective dimensions of dyspnea. One item assesses the immediate unpleasantness of dyspnea (A1) on a 0–10 visual numerical scale anchored by "neutral" (0) and "unbearable" (10). Five items assess dyspnea's sensory dimension and five items assess affective dimension of dyspnea, in terms of quality and intensity (on a scale of 0–10). Further, two scores are calculated: an "immediate perception domain" score (S), corresponding to the sum of A1 intensity plus intensities of the five sensory descriptors; and an "emotional response domain" score (A2), corresponding the sum of the five emotional descriptors [4,5].

Besides the assessment of dyspnea by the MDP, patients were assessed regarding pulmonary function (spirometry) and exercise capacity (6-minute walk test [6MWT]) following international guidelines and local reference values [9-12].

Furthermore, health status (COPD assessment Test - CAT)[3], anxiety and depression (Hospital Anxiety and Depression scale – HADS)[13] and dyspnea in daily life (Medical Research Council scale – MRC)[2] were also assessed and used as anchors.

Statistical analyses were performed with the SPSS Statistical Package 21.0 (IBM SPSS Statistics, Chicago, IL, USA). Normality in data distribution was evaluated using the Shapiro-Wilk test. Data were described as mean±standard deviation or median [interquartile range 25%-75%]. The concurrent validity was assessed by correlations of the MDP domains with CAT, HADS and MRC scores, using the Spearman correlation coefficient. Internal consistency was assessed by Cronbach's α. Inter- and intra-rater test-retest reliability was evaluated between all items and dimensions of the MDP using intraclass coefficient correlation (ICC). For Cronbach's α and ICC, values greater than 0.70 were considered satisfactory [14]. Significance level was set at $P<0.05$.

Sample size was calculated from the values proposed by Hulley et al.[15] based on the study by Silva et al.[3], expecting a minimum correlation of 0.60 between MDP and CAT, considering a two-sided alpha value of 0.05 and 80% of power. Hence, a minimum of 19 individuals were required.

Results and discussion

Thirty patients with COPD were included in the validation analysis (43% male, 63±8years, body mass index [BMI] 27±6Kg/m^2, forced expiratory volume in the first second [FEV_1] 48±15%predicted, six-minute walking test [6MWT] 464±84m and 84±16%predicted). However, 10 patients were excluded due to missing data from the reliability analysis, resulting in a sample of 20 subjects for this purpose (50%

male, 62±8years, BMI 27±6Kg/m^2, FEV_1 48±15%predicted, 6MWT 452±93m and 82±19%predicted). Both samples were similar regarding general characteristics (*P*>0,05 for all).

The Portuguese version of the MDP demonstrated moderate-strong correlations with *a priori* established anchors (i.e., CAT, HADS and MRC) (Table 1), similarly to French validation [7], strongly endorsing its use. Notably, concurrent validity was carried out against these instruments since they are widely used in COPD and measure dimensions similar to the MDP's composition.

Table 1. Concurrent validity of the Multidimensional Dyspnea Profile (MDP) with clinical instruments

MDP Variables	CAT Total	HADS Anxiety	HADS Depression	MRC
A1- Immediate unpleasantness	0.62*	0.68*	0.71*	0.55*
Breathing effort	0.59*	0.33	0.43*	0.44*
Air hunger	0.61*	0.45*	0.53*	0.53*
Chest tightness	0.55*	0.48*	0.59*	0.48*
Mental effort	0.63*	0.64*	0.64*	0.63*
Breathing a lot	0.37*	0.04	0.25	0.13
S- Immediate Perception				
Domain	0.75*	0.55*	0.71*	0.61*
Depression	0.44*	0.54*	0.52*	0.53*
Anxiety	0.75*	0.58*	0.66*	0.62*
Frustration	0.54*	0.52*	0.42*	0.52*
Anger	0.42*	0.44*	0.40*	0.34
Fear	0.26	0.32	0.52*	0.35
A2- Emotional Domain	0.74*	0.65*	0.66*	0.66*

Spearman correlation coefficient; **P*<0.05
CAT: COPD assessment Test; HADS: Hospital Anxiety and Depression scale; MRC: Medical Research Council Dyspnea scale.

Interestingly, the description "breathing a lot" was poorly correlated with all variables (Table 1). This may have happened because only 19% of patients reported

this descriptor, hindering its correlation with other variables. Likewise, Banzett et al. [6] unveil this sensation as being reported during induced-hyperpnea in heathy subjects. Indeed, the focus period in the present study was based on ADL (i.e., lower ventilatory burden); this could have mitigated this description by our patients. Moreover, CO_2 desensitization can also be hypothesized as a possible explanation [1,4].

The MDP was highly reliable, independently whether performed by the same or a different rater. The ICC intra-rater was: A1: 0.77 (0.48–0.90), S: 0.78 (0.52–0.91), and A2: 0.85 (0.66-0.94), with high internal consistency (Cronbach's α of 0.86, 0.88 and 0.92 respectively). Inter-rater analysis also demonstrated high correlations (ICC: A1: 0.74 (0.46–0.89), S: 0.75 (0.48–0.89) and A2: 0.91 (0.78-0.96) (Cronbach's α 0.85, 0.86 and 0.95 respectively).

These results have to be taken into account in light of study's strengths and limitations. Firstly, the sample for both analyses (validity and reliability) was larger than the minimum required sample size. The focus period of the present study (ADL in the last two weeks) and the intervals between time-points 1-2 and 3 (one to two weeks), followed specific recommendations provided by guidelines for reliability studies [16]. Moreover, patients' breathlessness was not affected since none of the patients experienced COPD exacerbations or other acute conditions during the study's period, and there were no changes in the scores of any of the anchors (data not shown). Not less important, despite translation was done according to the Portuguese language spoken in Brazil; we believe there is no limitation for its use in any Portuguese-speaking countries. Whether necessary, minor changes are possible without changing sentences' meaning. Furthermore, the MDP was not developed for a specific disease. Thus, as for other languages [5-7], the Portuguese

version can be used without adaptations for a wide spectrum of disease conditions, although specific validation is required.

Therefore, according to the present results it is possible to affirm that the Portuguese version of the MDP is the first valid and reliable instrument to assess the multidimensional dyspnea for Portuguese-speaking patients with COPD.

Acknowledgments

We would like to thank all the colleagues from the Laboratory of Research in Respiratory Physiotherapy for their support and assistance and the patients for agreeing to participate.

References

1. Parshall MB, Schwartzstein RM, Adams L, et al. An official American Thoracic Society statement: update on the mechanisms, assessment, and management of dyspnea. Am J Respir Crit Care Med 2012; 185:435–452.
2. Kovelis D, Segretti NO, Probst VS, Lareau SC, Brunetto AF, Pitta F. Validação do Modified Pulmonary Functional Status and Dyspnea Questionnaire e da escala do Medical Research Council para o uso em pacientes com doença pulmonar obstrutiva crônica no Brasil. J Bras Pneumol. 2008; 34:1008-1018.
3. Silva GPF, Morano MTAP, Viana CMS, Magalhães CBA, Pereira EDB. Validação do Teste de Avaliação da DPOC em português para uso no Brasil. J. Bras Pneumol. 2013; 39:402-408.
4. Banzett RB, O'Donnell CR, Guilfoyle TE, et al. Multidimensional Dyspnea Profile: an instrument for clinical and laboratory research. Eur Respir J 2015; 45: 1681–1691.

5. Meek PM, Banzett R, Parshall MB, et al. Reliability and validity of the multidimensional dyspnea profile. Chest 2012; 141:1546–1553.
6. Banzett RB, Pedersen SH, Schwartzstein RM, et al. The affective dimension of laboratory dyspnea: air hunger I more unpleasant than work/effort. Am J Respir Crit Care Med 2008; 177:1384–1390.
7. Morélot-Panzini C, Gilet H, Aguilaniu B, Devillier P, Didier A, Perez T, Pignier C, Arnould B and Similowski T. Real-life assessment of the multidimensional nature of dyspnoea in COPD outpatients. Eur Respir J 2016; 47:1668-1679.
8. Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017. Available from: http://goldcopd.org.
9. Miller MR, Hankinson J, Brusasco V, Burgos V, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J. 2005; 26:319-338.
10. Pereira CAC, Rodrigues SC, Sato T. Novos valores de referência para espirometria forçada em brasileiros adultos de raça branca. J Bras Pneumol. 2007; 33:397-406.
11. Holland AE, Spruit MA, Troosters T, Puhan MA, Pepin V, Saey D, et al. An Official European Respiratory Society / American Thoracic Society Technical Standard: Field Walking Tests in Chronic Respiratory Disease. Eur Respir J. 2014; 44:1428-1446.
12. Britto RR, Probst VS, de Andrade AF, Samora GA, Hernandes NA, Marinho PE, et al. Reference equations for the six-minute walk distance based on a Brazilian multicenter study. Braz J Phys Ther. 2013; 17:556-563.

13. Botega NJ, Bio MR, Zomignani MA, Garcia C, Jr., Pereira WA. [Mood disorders among inpatients in ambulatory and validation of the anxiety and depression scale HAD]. Rev Saude Publica. 1995; 29:355-363.
14. Nunnally JC, Bernstein IH. Psychometric theory. Third Edition. McGraw-Hill I, New York, 1994.
15. Hulley SB, Cummings SR, Browner WS, Grady DG, Newman TB. Delineando a pesquisa clínica. Uma abordagem epidemiológica. 3ª edição. Porto Alegre: Artmed; 2008.
16. Mokkink LB, Terwee CB, Patrick DL, Alonso J, Stratford PW, Knol DL, et al. The COSMIN checklist for assessing the methodological quality of studies on measurement properties of health status measurement instruments: An international Delphi study. Qual Life Res. 2010;19:539–549.

Supporting information

S1 Appendix. Multidimensional Dyspnea Profile: Portuguese and English versions.

S2 Appendix. Translation process and Linguistic validation of Portuguese version of the Multidimensional Dyspnea Profile.

S1 Appendix. Multidimensional Dyspnea Profile: Portuguese and English versions.

Perfil Multidimensional de Dispneia pag 90 de 4 nome/identificação_____data e hora

PERFIL MULTIDIMENSIONAL DE DISPNEIA

Roteiro para a primeira aplicação:

O objetivo deste questionário é nos ajudar a entender como você sente a sua respiração.

Não existem respostas certas ou erradas. Nós gostaríamos de saber o que você tem para nos dizer sobre a sua respiração.

Nesta página, nós lhe pedimos que nos diga o quão desagradável você sente a sua respiração. Na próxima página, nós lhe perguntaremos sobre a intensidade ou força das suas sensações ao respirar. A distinção entre esses dois aspectos relacionados à sensação ao respirar pode ser mais facilmente entendida se você se imaginar ouvindo um som, como de um rádio. Conforme o volume do som aumenta, eu posso lhe perguntar o quão alto isso lhe parece ou o quão desagradável é ouvir esse som. Por exemplo, uma música que você não gosta pode ser desagradável mesmo quando o volume está baixo, e pode se tornar ainda mais desagradável se o volume do som for aumentado. Da mesma forma, uma música que você gosta não se tornará desagradável mesmo se o volume do som for aumentado.

Escala A1

Use essa escala para graduar o **desagrado ou desconforto** da sua sensação ao respirar, quão **ruim** é (era) sua sensação ao respirar.

Por favor, foque durante o seguinte período_____

← ←	0	1	2	3	4	5	6	7	8	9	10
AGRADÁVEL	NEUTRO										INSUPORTÁVEL

Perfil Multidimensional de Dispneia pag 2 de 4 nome/identificação_____data e hora

Característica da Sensação (CS): Escolha

Abaixo encontram-se frases ou termos organizados em grupos com significado similar.

Passo 1: Marque cada grupo que descreve como é (era) a sua sensação ao respirar durante _____(indicar o período de tempo).

Passo 2: Por favor, marque também *um* grupo que melhor descreve como é (era) sua sensação ao respirar.

Se *QUALQUER* termo no grupo se aplicar, escolha esse grupo.	**Passo 1**		**Passo 2**
	NÃO SE APLICA	APLICA-SE	GRUPO QUE MELHOR DESCREVE
Minha respiração requer trabalho muscular ***ou*** esforço			
Eu não respiro ar suficiente ***ou*** eu me sinto sufocado ***ou*** eu sinto fome de ar			
Sinto meu peito e pulmões apertados ***ou*** restritos			
Minha respiração requer esforço mental ***ou*** concentração			
Eu estou respirando demais			

Perfil Multidimensional de Dispneia pag 3 de4 nome/identificação_____data e hora

Característica da Sensação (CS): Escalas

Use essas escalas para quantificar como é (era) a intensidade das suas sensações ao respirar (como a altura do som, independente do fato da sensação ser agradável ou desagradável. Por exemplo, uma sensação pode ser intensa sem ser desagradável).

Por favor, foque durante o seguinte período_____

Se QUALQUER termo no grupo se aplicar, classifique esse grupo.	**NENHUMA**										**O MAIS INTENSO QUE EU POSSO IMAGINAR**
Minha respiração requer trabalho muscular ***ou*** esforço	0	1	2	3	4	5	6	7	8	9	10
Eu não respiro ar suficiente ***ou*** eu me sinto sufocado ***ou*** eu sinto fome de ar	0	1	2	3	4	5	6	7	8	9	10
Sinto meu peito e pulmões apertados ***ou*** restritos	0	1	2	3	4	5	6	7	8	9	10
Minha respiração requer esforço mental ***ou*** concentração	0	1	2	3	4	5	6	7	8	9	10
Eu estou respirando demais	0	1	2	3	4	5	6	7	8	9	10
Outro*	0	1	2	3	4	5	6	7	8	9	10

*Caso ache necessário, você pode adicionar descrições da sua sensação ao respirar.

Perfil Multidimensional de Dispneia pag 4 de 4 nome/identificação_____data e hora

Escalas A2

Quando você sente que a sua respiração não está normal, você pode experimentar emoções ou "sentimentos". Usando as escalas abaixo, por favor, conte-nos sobre como suas sensações ao respirar fizeram você se sentir – classifique zero para qualquer emoção que você não tenha sentido.

Por favor, foque nas sensações durante o seguinte período_____.

	NENHUMA										**O MAIS INTENSO QUE EU POSSO IMAGINAR**
Deprimido	0	1	2	3	4	5	6	7	8	9	10
Ansioso	0	1	2	3	4	5	6	7	8	9	10
Frustrado	0	1	2	3	4	5	6	7	8	9	10
Com raiva	0	1	2	3	4	5	6	7	8	9	10
Com medo	0	1	2	3	4	5	6	7	8	9	10
Outro?	0	1	2	3	4	5	6	7	8	9	10

MULTIDIMENSIONAL DYSPNEA PROFILE

Script for first time use:

The purpose of this questionnaire is to help us understand how your breathing feels.

There are no right or wrong answers. We want to know what you tell us about your own breathing.

On this page we ask you to tell us how unpleasant your breathing feels. On a later page we will ask you about the intensity or strength of your breathing sensations. The distinction between these two aspects of breathing sensation might be made clearer if you think of listening to a sound, such as a radio. As the volume of the sound increases, I can ask you how loud it sounds or how unpleasant it is to hear it. For example, music that you hate can be unpleasant even when the volume is low, and will become more unpleasant as the volume increases; music that you like will not be unpleasant, even when the volume increases.

A1 Scale

Use this scale to rate the **unpleasantness or discomfort** of your breathing sensations, how **bad** your breathing feels [felt].

Please focus on the period when_____

← ←	0	1	2	3	4	5	6	7	8	9	10
PLEASANT	NEUTRAL										UNBEARABLE

SQ choice

Below are phrases or terms arranged in groups of similar meaning.

Step 1: Check each group that describes how your breathing feels [felt] during _____(indicate focus period).

Step 2: Please also mark *one* group that most accurately describes how your breathing feels [felt].

If *ANY* term in the group applies, choose that group.	**Step 1**		**Step 2**
	DOES NOT APPLY	DOES APPLY	MOST ACCURATELY DESCRIBES
My breathing requires muscle work ***or*** effort			
I am not getting enough air ***or*** I am smothering ***or*** I feel hunger for air			
My chest and lungs feel tight ***or*** constricted			
My breathing requires mental effort ***or*** concentration			
I am breathing a lot			

SQ Scales

Use these scales to rate the intensity of the breathing sensations you feel [felt] (like the loudness of sound, regardless of whether the sensation is pleasant or unpleasant; for example a sensation could be intense without being unpleasant.)

Please focus on the period when _____

If ANY term in the group applies, rate that group.	**NONE**										AS INTENSE AS I CAN IMAGINE
My breathing requires muscle work ***or*** effort	0	1	2	3	4	5	6	7	8	9	10
I am not getting enough air ***or*** I am smothering ***or*** I feel hunger for air	0	1	2	3	4	5	6	7	8	9	10
My chest and lungs feel tight ***or*** constricted	0	1	2	3	4	5	6	7	8	9	10
My breathing requires mental effort ***or*** concentration	0	1	2	3	4	5	6	7	8	9	10
I am breathing a lot	0	1	2	3	4	5	6	7	8	9	10
Other*	0	1	2	3	4	5	6	7	8	9	10

*If you need to, you can add additional descriptions of your breathing sensations.

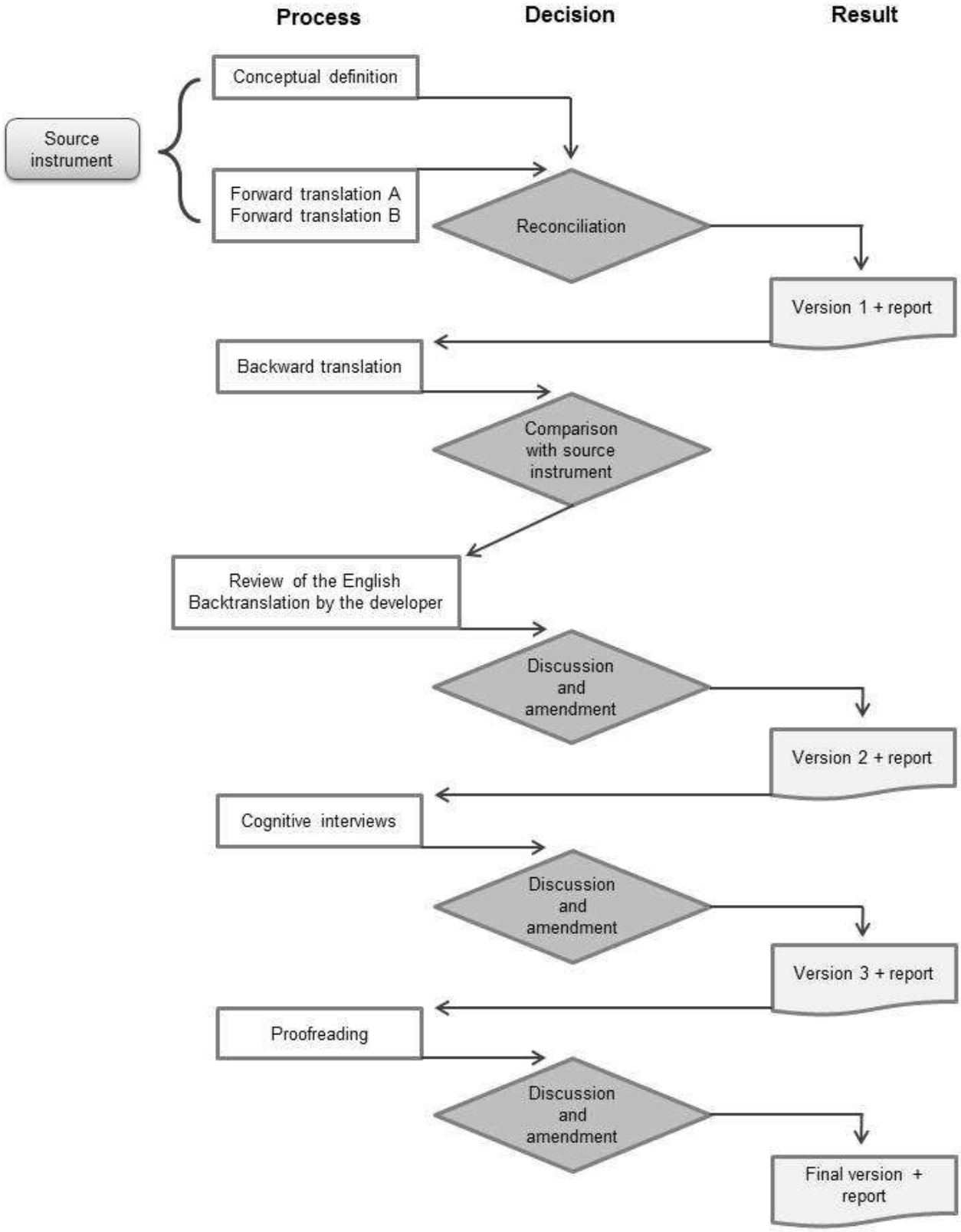
A2 Scales

When your breathing doesn't feel normal, you may experience emotions or 'feelings'. Using the scales below, please tell us about how your breathing sensations made you feel – rate zero for any emotion you did not feel.

Please focus on feelings during the period when _____.

	NONE										**THE MOST I CAN IMAGINE**
Depressed	0	1	2	3	4	5	6	7	8	9	10
Anxious	0	1	2	3	4	5	6	7	8	9	10
Frustrated	0	1	2	3	4	5	6	7	8	9	10
Angry	0	1	2	3	4	5	6	7	8	9	10
Afraid	0	1	2	3	4	5	6	7	8	9	10
Other?	0	1	2	3	4	5	6	7	8	9	10

S2 Appendix. Translation process and Linguistic validation of Portuguese version of the Multidimensional Dyspnea Profile.



5 GENERAL CONCLUSIONS

The articles presented in this thesis show that:

1. In the general population of older and mostly asymptomatic adults, resting lung function tests and routine assessments of activity-related shortness of breath (mMRC) and symptom burden (CAT), failed to discriminate people with pathophysiological abnormalities in the behavior of dynamic operating lung volumes during exercise and breathlessness as a LOSL. However, cardiopulmonary exercise testing is an alternative to identify these alterations, since those who complain of dyspnea as their LOSL have greater pulmonary alterations (such as lung volumes constrains) than people who stop for other reasons. Also, it was possible to establish that the main reason leading people with and without COPD diagnosis to stop exercising is leg fatigue alone or in combination with breathlessness.
2. In line with the most recent literature, the multidimensional aspects of dyspnea can be now assessed in Brazilians with COPD through the Multidimensional Dyspnea Profile. This instrument was translated and had its concurrent validation tested against widely used instruments. Also, it was shown to be reproducible even with different evaluators. Therefore, an useful instrument to assess the sensory and quality of dyspnea and the emotional aspect linked to this symptom is now available in Portuguese language.

ATTACHMENTS

ATTACHMENT A

Instructions for authors – Annals of the ATS

As an international online journal, the *Annals of the American Thoracic Society (AnnalsATS)*, covers adult and pediatric pulmonary medicine, respiratory sleep medicine, adult critical care medicine, and public health.

The mission of the *Annals of the American Thoracic Society (AnnalsATS)* is to improve the health of adults and children with respiratory diseases, sleep disorders, and critical illness through dissemination of research and clinician education.

The goals of the journal are:

- To disseminate new information arising from high-quality clinical, epidemiological, and health services research related to respiratory, sleep, critical care medicine, and population health
- To educate pulmonary, sleep, and critical care providers about clinical care
- To publish commentary on public health, environmental health, global health, and health policy relevant to ATS members

Formatting Notice:

AnnalsATS does not require a specific format for initial submissions of Original Research manuscripts. A title page that includes author names, author affiliations, and contact information for the corresponding author are the only requirements. Consecutive line numbers throughout are suggested, but not required. Revised Original Research manuscripts and all other manuscript types must adhere to our formatting criteria.

Article Categories

Section	Description	Target Length	Abstract	Illustrations, References, and Other Notes
Original Research	Full-length reports of original research, including meta-analyses. Manuscripts do not require specific formatting upon initial submission.	3,500 words(excluding abstract, references, and legends)	Structured Up to 350 words	Up to 60 references

Manuscript Preparation: Specific Article Types

Original Research Articles

AnnalsATS particularly welcomes the following types of submissions: clinical trials, observational studies (e.g., cohort studies, case-control studies), epidemiological studies of population and community health and disease, studies of diagnostic tests, cost-effectiveness analyses, decision analyses, meta-analyses, and qualitative research. Manuscripts that do not adhere to rigorous methodology and those that generate only incremental new knowledge will not be considered for publication.

NOTE: Descriptive reports of disease entities are unlikely to be accepted unless such reports are paradigm-shifting, describe newly discovered diseases, or have other novel elements. A large sample size will typically be an unacceptable justification for descriptive reports. Case reports and case series will also not be published in *AnnalsATS* unless they meet similar criteria.

Critical Guidance for Original Research Articles

Introduction

The introduction should be brief and provide an adequate background for clinical oriented readers to understand the context and rationale for the reported study. The objective of the study and a testable hypothesis should be stated.

Methods

The Methods section should provide the reader with a transparent explanation of the conduct and analysis of the study, including descriptions of how the participants were selected, the dates and setting(s) of the study, data sources used, study design, interventions/exposures, diseases/outcomes, covariates considered and included, participant follow-up (if any), and the statistical analysis used to analyze the data.

A Working Group of editors of respiratory, critical care, and sleep journals has **published guidance** on appropriate and inappropriate analytic methods for observational causal inference studies, such as cohort, case-control, and cross-sectional studies. Authors are strongly urged to be familiar with the requirements enumerated in **Key Principle #1** of this document. In particular:

1. Papers reporting the results of observational causal inference studies should include a detailed plan for how potential confounding factors were handled. Causal inference studies that do not account for confounding factors are unlikely to be accepted.
2. Confounders should be defined based on mechanistic and biological knowledge, with a strong preference for use of directed acyclic graphs as described in **Key Principle #1**. Covariate selection should not be based on

statistical hypothesis testing, changes in effect estimates, model fit, or any stepwise methods.

3. Do not condition on or adjust for effects of either the exposure or the outcome. Attention should be paid to avoiding collider bias.
4. A directed acyclic graph can be presented in the supplement if desired.
5. The following methods are strongly discouraged:
    A. P-value– or model-based variable selection methods
    B. Variable selection based on beta-coefficient changes
    C. Selection of variables to identify multiple “independent predictors”

When constructing **prediction models**, variable selection methods should be appropriate to the study design. Modern variable selection methods are favored. These include (but are not limited to) shrinkage, penalized maximum likelihood estimation, and machine learning. P-value–based selection methods (e.g., stepwise selection) are discouraged (unless the paper includes validation of the prediction model in an external cohort). Authors should ensure that they address basic prediction model issues such as overfitting, optimism, missingness, interactions, model assumptions, and linearity. Authors are referred to **Ewout Steyerberg’s textbook on Clinical Prediction Models** for additional guidance.

Results

AnnalsATS has a preference against presenting P values. The journal subscribes to the six principles of P values espoused by the American Statistical Association. For studies with small sample sizes, if statistical hypothesis testing is performed, nonparametric testing (e.g., Wilcoxon rank sum tests, and Kruskal-Wallis test followed by Dunn’s or Friedman’s test) should be used. Results of statistical tests for “normality” will not be accepted as a rationale for using t-tests, ANOVA, and other similar statistical hypothesis tests that assume a normal distribution. Handling of missing data should be explicitly described.

A table of participant characteristics should be included in most manuscripts. In most cases, the authors should display participant characteristics stratified by the primary measure of exposure (i.e., risk factor of interest). One notable exception is in reporting the results of a case-control study, which should include separate columns for each case and control group. P values comparing baseline characteristics should not be presented unless you have *a priori* hypotheses about these comparisons, which will require justification. If desired, p values for these comparisons can be included in the online supplement.

We suggest reporting associations between exposure(s) and outcome(s) in Tables or Forest Plots. Suggested examples follow. In Tables A–D, more than one outcome can be presented (“Outcome 1”, “Outcome 2”, etc.). In Table E, more than one exposure can be presented (“Exposure 1”, “Exposure 2”, etc.). P values in these tables are entirely optional (see below).

Associations of a categorical exposure (Table A) or a continuous exposure (Table B) with a categorical outcome. (See Table E for case-control studies). Tables A and B can be adapted to present risks (or prevalences) by removing the "person-years" row and by replacing the word "rate" with either "risk" or "prevalence", as appropriate. When using models that report odds ratios, adjusted odds ratios can be reported instead of adjusted risk ratios. However, we still prefer to see "risk" (or "prevalence") and "unadjusted risk ratio" (or "unadjusted prevalence ratio") in the table rather than "odds" and "unadjusted odds ratios." Please note that binomial regression with a log link (or alternatively, Poisson regression with robust standard error estimation) can be used to generate adjusted risk ratios (or prevalence ratios) instead of odds ratios in the absence of case-control sampling. See **the following article**. In addition, for categorical exposures, confidence intervals for rate/risk/prevalence ratios should only be presented when these categories are of biological or clinical relevance. Table A shows a 4-level categorical variable. The table can be adapted to any categorical variable with any number of levels. It can also be used when dividing a continuous exposure into quantiles or other categories.

All quantitative results must be defined when presented (e.g., mean, standard deviation, odds ratio). Units (e.g., years, mL, ng/dL) should be included in the presentation of quantitative information.

Consider the study's sample size when determining the precision used to present results. For example, in small studies, rounding results to 2 or 3 decimal places may be inappropriate (depending on the units of the variables), whereas in large studies rounding to 0 or 1 decimal places may be insufficient. Percentages should rarely include more than 1 decimal place.

The results obtained by testing the primary hypothesis should be presented before other analyses. All effect estimates should be accompanied by a measure of precision (such as a confidence or credible interval). *AnnalsATS* has a preference against presenting P values. A notable exception is a P value for interaction. If P values are presented, they should have accompanying effect estimates and confidence/credible intervals. When presented, P values should be rounded to 2 decimal places, unless < 0.01 or when the P value approximates 0.05, in which case 3 decimal places is reasonable. Exceptions will be made in specific circumstances (e.g., genomic research).

In observational causal inference studies, do not present all of the effect estimates from a model designed to test a single causal association ("Table 2 fallacy"). If desired, these results may be presented in the online supplement.

AnnalsATS advises against using the vague labels "significant" and "nonsignificant," which lead readers (and authors) to implicitly conclude that an association is present or absent. Use of the unqualified word "significant" tends to blur the important distinction between statistical significance and clinical significance. Instead, simply report the quantitative findings as indicated above. The clinical, mechanistic, or biological interpretations of effect sizes provide greater value and should be used in place of these labels.

Visual Presentation of Results

Authors should take a thoughtful and careful approach to the visual presentation of quantitative results in figures. When possible, presentation of individual data points should accompany measures of central tendency and variation. For example, box plots should include an overlay of individual datapoints. The “data–ink ratio” should be maximized by avoiding unnecessary lines, grids, and text. Abbreviations should be used sparingly. Continuous data should not be presented in bar charts with standard error bars (“plunger plots”). Authors should use color-blind friendly palettes. Figures presenting log-transformed data should display nontransformed data on a logarithmic scale.

Discussion/Conclusions

The Discussion should begin with a summary of the key findings of the study and should place the current study in the context of existing literature on the topic. Potential explanations for the findings, including both mechanisms and threats to validity (such as confounding and bias), as well as limitations of the work should be discussed. A concluding paragraph can place the work in clinical context. Writing should be concise and remain focused on the study methodology and results.

Causal language (e.g. 'leads to', 'results in', 'has an effect on',) should only be used to describe results of studies that support causal interpretations. In such cases, authors should clearly describe any underlying assumptions and design-specific threats to causal inference.

When such assumptions and threats cannot be tested or otherwise addressed, authors are encouraged to adopt associational interpretations. Such studies remain of great potential interest to the journal, particularly when they establish compelling evidence of relationships that warrant further study.

ATTACHMENT B

Submission guidelines to PLOS ONE

Style and Format

1. **2.**	**12**	Manuscript files can be in the following formats: DOC, DOCX, or RTF. Microsoft Word documents should not be locked or protected. LaTeX manuscripts must be submitted as PDFs. Read the LaTeX guidelines.
3.	**Length**	Manuscripts can be any length. There are no restrictions on word count, number of figures, or amount of supporting information. We encourage you to present and discuss your findings concisely.
4.	**Font**	Use a standard font size and any standard font, except for the font named “Symbol”. To add symbols to the manuscript, use the Insert → Symbol function in your word processor or paste in the appropriate Unicode character.
5.	**Headings**	Limit manuscript sections and sub-sections to 3 heading levels. Make sure heading levels are clearly indicated in the manuscript text.
6.	**Layout and spacing**	Manuscript text should be double-spaced. Do not format text in multiple columns.
7.	**Page and line numbers**	Include page numbers and line numbers in the manuscript file. Use continuous line numbers (do not restart the numbering on each page).
8.	**Footnotes**	Footnotes are not permitted. If your manuscript contains footnotes, move the information into the main text or the reference list, depending on the content.
9.	**Language**	Manuscripts must be submitted in English. You may submit translations of the manuscript or abstract as supporting information. Read the supporting information guidelines.
10.	**Abbreviations**	Define abbreviations upon first appearance in the text. Do not use non-standard abbreviations unless they appear at least three times in the text. Keep abbreviations to a minimum.
11.	**Reference style**	PLOS uses “Vancouver” style, as outlined in the ICMJE sample references. See reference formatting examples and additional instructions below.
12.	**Equations**	We recommend using MathType for display and inline equations, as it will provide the most reliable outcome. If this is not possible, Equation Editor or Microsoft's Insert→Equation function is acceptable. Avoid using MathType, Equation Editor, or the Insert→Equation

	function to insert single variables (e.g., “$a^2 + b^2 = c^2$”), Greek or other symbols (e.g., β, Δ, or ′ [prime]), or mathematical operators (e.g., x, ≥, or ±) in running text. Wherever possible, insert single symbols as normal text with the correct Unicode (hex) values. Do not use MathType, Equation Editor, or the Insert→Equation function for only a portion of an equation. Rather, ensure that the entire equation is included. Equations should not contain a mix of different equation tools. Avoid “hybrid” inline or display equations, in which part is text and part is MathType, or part is MathType and part is Equation Editor.

Manuscript Organization

Manuscripts should be organized as follows. Instructions for each element appear below the list.

Beginning section	*The following elements are required, in order:* • Title page: List title, authors, and affiliations as first page of the manuscript • Abstract • Introduction
Middle section	*The following elements can be renamed as needed and presented in any order:* • Materials and Methods • Results • Discussion • Conclusions (optional)
Ending section	*The following elements are required, in order:* • Acknowledgments • References • Supporting information captions (if applicable)
Other elements	• Figure captions are inserted immediately after the first paragraph in which the figure is cited. Figure files are uploaded separately. • Tables are inserted immediately after the first paragraph in which they are cited. • Supporting information files are uploaded separately.