EFFECT OF EXPIRATORY AIRFLOW LIMITATION ON INCREMENTAL EXERCISE CAPACITY AND BREATHING RESPONSES DURING TREADMILL EXERCISE IN HEALTHY INDIVIDUALS

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ABSTRACT

RATIONALE: Individuals with chronic obstructive pulmonary disease (COPD) have expiratory flow limitation (EFL) due to obstruction of the airways. Such individuals typically experience dyspnea on exertion and exercise intolerance. A Starling resistor (SR) can be used to simulate the EFL as occurs in COPD in order to evaluate its effect on exercise capacity. Although the SR has been evaluated during bicycle exercise, no studies have studied its effect during incremental treadmill walking.

OBJECTIVES: The objective of the current study was to evaluate the effect of EFL, created by using a SR, on exercise capacity, metabolic parameters, breathing pattern, and exercise limiting symptoms in healthy participants during incremental treadmill exercise.

METHODS: Healthy non-smoking individuals with no remarkable medical history were recruited in this cross-sectional repeated measures study. Participants performed two randomized incremental symptom-limited treadmill walking tests with and without a SR until exhaustion. Peak exercise workload (WLpeak) was assessed as the maximum exercise workload that was achieved and maintained during the last 30 seconds of exercise. Breathing pattern and metabolic parameters were measured breath-by-breath using a Vmax metabolic cart. Inspiratory capacity (IC) and Borg ratings of dyspnea and leg fatigue were measured every minute during exercise.

RESULTS: Fifteen individuals (4 males, 11 females) aged 27 ± 12 years (mean ± SD) participated in the study. Mean expiratory flow with the SR was 0.5 ± 0.1 L/s (mean ± SD). Compared to treadmill exercise without the SR (no EFL), exercise with the SR resulted in a significantly lower WLpeak, as well as a lower peak minute ventilation, O_2 uptake and CO_2 production ($P<0.001$ for all). Tidal volume, which increased progressively during exercise with and without the SR, was observed to drop at end-exercise with the SR. The lower tidal volume at higher workloads was associated with an increased respiratory rate and a decreased IC indicating dynamic hyperinflation at end-exercise. Dyspnea was reported as the dominant exercise limiting symptom with the SR, while leg fatigue was the dominant symptom reported in the absence of EFL.

CONCLUSION: During treadmill exercise, EFL resulted in a reduced exercise performance and severe dyspnea as exercise intensity increased. A SR can simulate in healthy individuals the exercise limitations that are typically observed in COPD.

Key words: Exercise, Starling Resistor, Treadmill, Chronic Obstructive Pulmonary Disease.

ABRÉGÉ

JUSTIFICATION: Les personnes atteintes de maladie pulmonaire obstructive chronique (MPOC) ont une limitation du débit expiratoire (EFL) à cause de l'obstruction des voies respiratoires. Ces personnes souffrent généralement de dyspnée à l'effort et de l'intolérance à l'exercice. Une résistance Starling (SR) peut être utilisée pour simuler l'EFL qui se produit dans la MPOC afin d'évaluer son effet sur la capacité d'exercice. Bien que le SR ait été utilisé pendant l'exercice à vélo, aucune étude n'a évalué son effet pendant la marche progressive sur tapis roulant.

OBJECTIFS: L'objectif de l'étude était d'évaluer l'effet de l'EFL créé en utilisant un SR, sur la capacité d'exercice, les paramètres métaboliques, le schéma respiratoire et les symptômes limitant l'exercice chez les mêmes participants au cours d'un exercice progressif sur tapis roulant.

MÉTHODES: Des personnes non-fumeuses en bonne santé sans historique médical significatif ont été recrutées dans cette étude transversale à mesures répétées. Les participants ont effectué deux tests de marche sur tapis roulant aléatoires progressifs aux symptômes limités avec et sans SR jusqu'à épuisement. La charge de travail maximale à l'exercice (WLpeak) a été évaluée comme étant la charge de travail maximale réalisée et maintenue au cours des 30 dernières secondes de l'exercice. Le profil respiratoire et les paramètres métaboliques ont été mesurés respiration par respiration à l'aide d'un chariot métabolique Vmax. La capacité inspiratoire (CI), ainsi que les évaluations de la dyspnée et de la fatigue des jambes sur l'échelle de Borg ont été mesurées pendant l'exercice.

RÉSULTATS: Quinze individus (4 hommes, 11 femmes) âgés de 27 ± 12 ans (moyenne ± ET) ont participé à l'étude. Le débit expiratoire moyen avec le SR était de 0.5 ± 0.1 L/s (moyenne ± écart-type). Par rapport à l'exercice sur tapis roulant sans SR (pas d'EFL), l'exercice avec le SR a entraîné un WLpeak significativement plus faible, ainsi qu'une ventilation minute de pointe inférieure, l'absorption d'O2 et la production de CO2, ($P < 0.001$ pour tous). On a observé que le volume courant, qui augmentait progressivement pendant l'exercice avec et sans le SR, diminuait à la fin de l'exercice avec le SR. Le volume courant plus faible à des charges de travail plus élevées était associé à une augmentation de la fréquence respiratoire et une diminution de la capacité inspiratoire indiquant une hyperinflation dynamique à la fin de l'exercice. La dyspnée a

été signalée comme le symptôme dominant limitant l'exercice avec le SR, tandis que la fatigue des jambes était le symptôme dominant rapporté en l'absence d'EFL.
CONCLUSION: Au cours de l'exercice sur tapis roulant, l'EFL a entraîné une réduction de la performance à l'exercice et une dyspnée sévère à mesure que l'intensité de l'exercice augmentait. Il est possible de simuler la limite de l'exercice et les anomalies physiologiques de la MPOC sur tapis roulant par l'application d'un SR.
Mots clés: exercice, résistance Starling, tapis roulant, maladie pulmonaire obstructive chronique.

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PREFACE

This research was designed to contribute to knowledge in Chronic Obstructive Pulmonary Disease (COPD), to provide guidance for further research in respiratory physiology and rehabilitation, and ultimately to help improve the quality of life of individuals with COPD. Such individuals typically experience exercise intolerance which limits their physical activity, thereby worsening peripheral skeletal muscle function and contributing to poor quality of life. In this study, we used a mechanical device called a Starling resistor (SR) to mimic, in healthy individuals, the expiratory flow limitation (EFL) that occurs in COPD. This study evaluated the effect of this externally imposed EFL on exercise performance and physiological responses during incremental treadmill walking. It was anticipated that the exercise responses generated during treadmill walking with the SR, would be comparable to those previously reported in participants evaluated with bicycle ergometry, although this to date had not been validated.

This research was conducted during the Coronavirus-19 (COVID-19) pandemic. The data that we used in the current study involved the first component of a study titled "*Evaluation of Arm Loading on Walking Endurance and Breathing Response in Simulated COPD Patients: An Exploratory Physiological Cross-Sectional Trial"* which was conducted by students from the School of Physical and Occupational Therapy (SPOT), McGill University, under the supervision of Dr. Jadranka Spahija. Due to the COVID-19 pandemic, the original study for my graduate thesis entitled "*Role of Respiratory and Upper Limb Muscle Strength and Endurance in Upper Limb Exercise Performance in Individuals with COPD*" which I was in the process of conducting was stopped due to the restrictions which were imposed on in-person clinical research. After careful consideration and approval from the SPOT Graduate Program Director, my research project was replaced with a study consisting of a secondary analysis of incremental exercise test data which had been acquired as part of the aforementioned study and which was only used to establish the exercise intensity needed for the treadmill endurance tests that were carried out in the arm loading study. The data analysis and manuscript which is included in this thesis represents work that is distinct of the data analysis and manuscript that encompasses the arm loading study.

This thesis contains five chapters. Chapter one contains an introduction. Chapter two and three contain the review of literature. Chapter four contains the rationale of the study. Chapter five contains the formatted manuscript and conclusion.

CONTRIBUTION OF AUTHORS

My thesis supervisor, Dr. Jadranka Spahija, supervised and contributed to all stages of this research project, including the initial conception and design of the protocol, supervision and advice to students during participant recruitment and data collection, guidance for the data analysis and interpretation of the findings, as well as the revision of all components of this thesis. Meihua Li was the first author responsible for data analysis and manuscript writing. Matei Cotoros, Anita Mahi, Shirin Patel and Tianqing Wei contributed to the study design, participant recruitment and the running of the study.

LIST OF ABBREVIATIONS

Abbreviation	Meaning
CO_2	Carbon dioxide
DH	Dynamic hyperinflation
EELV	End-expiratory lung volume
EFL	Expiratory flow limitation
EILV	End-inspiratory lung volume
ERV	Expiratory reserve volumes
FEV_1	Forced expiratory volume in the first second
FRC	Functional residual capacity
FVC	Forced vital capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HR	Heart rate
HRQoL	Health-related quality of life
IC	Inspiratory capacity
IRV	Inspiratory reserve volume
NSR	Non-Starling resistor
$P_{ET}CO_2$	Partial pressure of end-tidal carbon dioxide
RR	Respiratory rate
RV	Residual volume
SpO_2	Oxygen saturation
SR	Starling resistor
Te	Expiratory time
Ti	Inspiratory time
Ti/Ttot	Duty cycle
TLC	Total lung capacity
Ttot	Total breath time

VCO_2	Carbon dioxide production
VCO_2/VO_2	Respiratory exchange ratio
VD	Dead space
VE	Minute ventilation
VE/VO_2	Ventilatory equivalents for oxygen
VO_2	Oxygen consumption
VT	Tidal volume
VT/Ti	Mean inspiratory flow
VT/Te	Mean expiratory flow
WL	Workload
WLpeak	Peak workload

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CHAPTER I. INTRODUCTION

Chronic obstructive pulmonary disease (COPD), which is a respiratory condition characterized by airflow limitation, is currently the fourth leading cause of mortality worldwide [1-3]. Air pollution, noxious gases and particles, accelerated aging, gender, and genetic abnormalities, have been identified as risk factors contributing to the development of the disease [2, 4, 5]. The most significant and well-studied risk factor for COPD is long-term cigarette smoking [2, 6]. Respiratory symptoms commonly reported by individuals with COPD include dyspnea at rest or on physical exertion, cough, and sputum production [2]. COPD is characterized by an abnormal inflammation of the airways and destruction of the lung parenchyma which results in narrowing of the airways [3]. The resulting expiratory flow limitation (EFL) and gas trapping contribute to a reduction in exercise tolerance and a vicious cycle of physical inactivity that can lead to poor health-related quality of life (HRQoL) and a higher rate of mortality [3, 7, 8]. COPD continues however to be under-diagnosed and under-treated [9], and estimates of its prevalence may be underestimated [10]. Further efforts are therefore still needed to optimize the management of the disease in such individuals in order to alleviate the adverse symptoms and improve HRQoL [11].

Individuals with COPD are limited in their ability to perform exercise as a result of EFL [12, 13]. Numerous studies have evaluated the mechanisms underlying the exercise intolerance in COPD, especially when performing lower limb exercise [12, 13]. Exercise impairment in COPD has been directly associated with ventilatory limitation [14]. Dyspnea, which is a subjective sensation of breathlessness, is the primary symptom that limits exercise capacity in COPD [15, 16], and dynamic hyperinflation (DH) which often occurs during exercise can contribute to the dyspnea and exercise intolerance that is experienced [17, 18]. In addition to ventilatory impairment, individuals with COPD also exhibit respiratory and peripheral muscle dysfunction, associated with various factors including a reduction in the oxidative metabolism, muscle atrophy, and a shift in the muscle fiber-types [19, 20]. There is also evidence that leg muscle fatigue, induced by peripheral muscle dysfunction, can limit exercise performance in such individuals [13, 16]. The physiological responses for different types of lower limb exercise, including walking and cycling have been evaluated in individuals with COPD. Dyspnea, which

is a major exercise limiting symptom, has been reported to be higher during walking than cycling exercise [21-24]. However, there is evidence that the quadriceps muscles are more extensively used during lower limb cycling than treadmill walking, resulting in a higher level of leg fatigue with leg cycling [21, 22]. Other parameters such as partial pressure of end-tidal carbon dioxide ($P_{ET}CO_2$), ventilatory equivalents for oxygen (VE/VO_2), respiratory exchange ratio (VCO_2/VO_2) have been reported to be lower during walking exercise compared to cycling exercise [22, 23, 25, 26].

Studies have previously used a SR applied to the expiratory phase of breathing in order to simulate in healthy participants the EFL that is experienced by individuals with COPD [27-29]. The SR is a device that consists of a collapsible tube inside of a rigid chamber, whereby expiration results in partial collapse of the tube, preventing an increase in the expiratory flow despite any increases in expiratory effort [30]. There is evidence that healthy participants experience high exertional dyspnea, reduced exercise capacity, carbon dioxide (CO_2) retention and abnormal circulation during leg cycling exercise with a SR [28-32], reproducing the important exercise responses observed in COPD [33-35].

To the best of our knowledge, no studies to date have evaluated the physiological effects of breathing through a SR, during incremental treadmill exercise in healthy individuals. However, several studies have compared the exercise responses to treadmill and cycling exercise in individuals with COPD [36-38]. It remains unknown to what extent the different types of exercise affect the results with the application of a SR during exercise in healthy individuals, and if the SR can successfully simulate the important features of COPD during treadmill exercise.

Therefore, the purpose of this study was to evaluate the effect of an imposed EFL by the application of a SR on peak workload (WLpeak), breathing pattern, metabolic parameters and exercise limiting symptoms during incremental treadmill exercise in healthy individuals.

CHAPTER II. LITERATURE REVIEW

2. CHRONIC OBSTRUCTIVE PULMONARY DISEASE

2.1 Definition, Diagnose and Classification of COPD

COPD is a respiratory condition that is characterized by persistent respiratory symptoms and airflow limitation that is not fully reversible [1, 2]. It is associated with persistent airway inflammation, destruction of the lung parenchyma and dynamic airway collapse, as well as remodelling of the lung vasculature [39, 40]. Although air pollution, noxious gases and particles may contribute to the development of COPD, cigarette smoking is the most significant risk factor, having been identified as the causal factor in more than 90% of individuals diagnosed with COPD [4, 5]. Genetic factors and other environmental risk factors also play important roles in determining the disease, given that only about 15% of smokers develop symptomatic COPD [5, 41, 42].

The most common symptoms characterizing COPD are exertional dyspnea, cough and sputum production [2], which can lead to a vicious cycle of physical inactivity during daily life and can have negative effects on HRQoL [15, 43]. Moreover, other factors such as inhalation of environmental irritants, bronchiolitis, viral or bacterial infections, mucosa hyperemia in the small airways, viral infections, bacterial infections, discontinuation of medications or diet deviation can also contribute to the exacerbation of COPD [44].

According to The Global Initiative for Chronic Obstructive Lung Disease (GOLD), spirometry along with an appropriate history are required for the diagnosis of COPD [2, 45]. The presence of persistent airflow limitation is confirmed by a post-bronchodilator ratio of forced expiratory volume in the first second to the forced vital capacity (FEV_1/FVC) of less than 70% [2]. Individuals with COPD commonly have a decreased FEV_1 as well as FVC. When routine spirometry is unavailable, a peak expiratory flow rate of < 80% predicted can detect over 90% of patients with COPD, and because of ease of use, can be used to detect patients with COPD in the

community [46]. Peak expiratory flow, however, does not correlate well with the results of spirometry [47-49] and has an appreciable false positive rate [46]. Therefore, spirometry remains the standard and recommended tool for COPD diagnosis [2]. Worth mentioning, however, is that spirometric parameters have been shown to correlate poorly with symptom intensity, exercise tolerance and HRQoL [50]. Moreover, spirometry does not provide a full measurement of lung volumes. Therefore, complete pulmonary function testing along with questionnaires designed to evaluate the HRQoL are recommended as assessments to define COPD and facilitate the diagnosis of the disease [2, 50-52].

According to the GOLD criteria, severity of airflow limitation in COPD is based on post-bronchodilator FEV_1 values, and is divided into four classes: mild, moderate, severe, and very severe. This GOLD classification of COPD disease severity, shown in Table 2.1, is also supported by the American Thoracic Society (ATS) and European Respiratory Society (ERS) [53].

CLASSIFICATION OF AIRFLOW LIMITATION SEVERITY IN COPD (BASED ON POST-BRONCHODILATOR FEV_1)	
In patients with $FEV_1/FVC < 0.70$:	
GOLD 1: Mild	$FEV_1 \geq 80\%$ predicted
GOLD 2: Moderate	$50\% \leq FEV_1 < 80\%$ predicted
GOLD 3: Severe	$30\% \leq FEV_1 < 50\%$ predicted
GOLD 4: Very Severe	$FEV_1 < 30\%$ predicted

Table 2.1. Spirometric classification of COPD.

FEV_1: forced expiratory volume in the first second, FVC: forced vital capacity. Adapted from The GOLD Guidelines [2].

2.2 Epidemiology of COPD

2.2.1 Prevalence

According to the Global Burden of Disease published by the World Health Organization, an estimated 63.3 million people around the world suffer from COPD [54]. It was reported that 772,200 (4%) of Canadians aged 35 and older were diagnosed with COPD from 2009 to 2010 [55]. Based on more recent data collected by the Canadian Health Measures Survey (CHMS) [56] and by the Canadian Community Health Survey (CCHS), the total number of individuals with COPD in Canada over the age of 35 years in 2018 reached 847,300 [57]. Estimates from a study which looked at the effects of age and sex variation of Canadians revealed that 16.7% of the population met a GOLD stage 1 classification or higher [58]. In another study by the Canadian Lung Association, approximately 1.5 million Canadians were found to be affected by COPD, with another estimated 1.5 million being undiagnosed [59]. In addition, males were reported to have a lower prevalence in comparison to females in all age groups, except for those who were 75 years and older [60]. However, current estimates may underestimate the actual prevalence of COPD. According to Evans et al. in 2014 [10], estimates were based on individual self-reports of having been diagnosed by health-care professionals without supporting evidence of actual lung function measurements. It is therefore suspected that the prevalence of COPD could be 5~15% higher than has been reported among Canadians aged 35 to 79 [10].

2.2.2 Morbidity and Mortality

COPD is a major cause of global morbidity and mortality [61-63], accounting for around 3 million deaths annually [61]. Currently, it is the fourth leading cause of death in the world [64, 65]. Its contribution to global mortality is expected to increase by 30% in the next several years and it is projected to become the third leading cause of death by 2020 [2, 66]. The mortality rate in individuals with COPD has increased over the years [64]. It is estimated that around 3.2 million people died from COPD worldwide in 2015, accounting for 5% of the total annual deaths globally [67]. A study that looked at a period from 1980 to 1995 found a significant increase in the mortality rate (doubled numbers) in females with COPD, while it remained relative stable

among males [68]. In 2003, an estimated 5,366 males and 4,503 females died from COPD in Canada [58]. There is evidence that the morbidity of COPD increases with increasing age as well as the presence of other comorbid chronic conditions [69], and is worse in males than in females [3, 70].

2.2.3 Burden of COPD

COPD results in a significantly economic and social burden and is one of the leading causes in the burden of diseases globally [2]. In the United States, direct costs of hospitalization for COPD are estimated to be over $18 billion annually [71], while in Canada, the total cost of hospitalization is about $1.5 billion per year [72]. To provide a consistent measures of disease burden worldwide, the authors of the Global Burden of Disease (GBD) used The Disability-Adjusted Life Year (DALYs) metric to identify the severity of disability [73], which is a combination of years lost due to mortality and years lived with disability due to the disease [66]. In previous studies by GBD, COPD ranked eighth in 2005 among the leading causes of DALYs lost globally, while in 2013 it was fifth as the leading cause of DALYs lost [2, 74].

2.3 Pathophysiology of COPD

2.3.1 Operating Lung Volumes

As mentioned above, complete pulmonary function testing (PFT), including spirometry (FEV_1 and FVC) and lung volume measurement, should be performed on individuals with COPD. Figure 2.1 illustrates the operating lung volumes for healthy individuals and those with different levels of COPD disease severity. As illustrated, individuals with COPD exhibit a larger residual volume (RV), functional residual capacity (FRC), and total lung capacity (TLC) which are associated with greater lung impairments in terms of loss of elastic recoil, lung parenchyma changes, and air trapping [75]. The inspiratory capacity (IC) which is the maximum volume of air that can be inspired after a normal expiration, and is composed of the inspiratory reserve volume (IRV) and the tidal volume (VT), is observed to decrease in COPD primarily because of

a reduction in the IRV due to increases in the FRC, given that VT remains unchanged from that observed in healthy individuals [75].

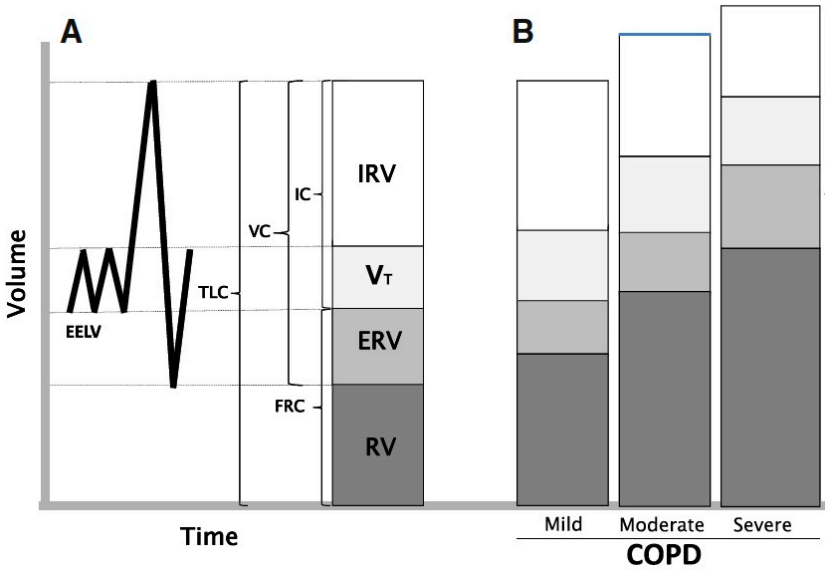

Figure 2.1. Operating lung volumes and capacities in healthy individuals and COPD patients. The lung volume parameters that are measured include total lung capacity (TLC), vital capacity (VC), residual volume (RV), functional residual capacity (FRC), inspiratory reserve volumes (IRV), expiratory reserve volumes (ERV), tidal volume (VT), and inspiratory capacity (IC). In individuals with COPD, IC represents the limits for expanded VT as a result of EFL. Meanwhile, FRC is increased as a result of an increased RV. By Sanguinetti. (2014) [76].

2.3.2 Expiratory Flow Limitation (EFL)

The respiratory system is an elastic structure that can change shape when there is a distorting force. In healthy individuals with a normal respiratory system compliance and a functional ventilatory pump, gas exchange occurs normally to maintain ventilation and is able to meet the metabolic needs of the body. During inspiration, the chest wall expands in response to activation and contraction of the diaphragm and external intercostal muscles, which decreases intrapleural pressure and brings air into the lungs [77]. In contrast, expiration is typically a passive process

accomplished by using the elastic recoil energy that is stored in the lungs and chest wall in the preceding inspiration [78]. In individuals with COPD, airflow limitation can result from emphysema (i.e. destruction of the lung parenchyma) or chronic obstructive bronchiolitis (i.e. inflammatory narrowing of small airways) [2, 77]. The destruction of lung parenchyma involves loss of alveolar attachments [79] and destruction of the alveolar walls, which decreases the total surface area of the lungs [80]. The exaggerated chronic inflammation which can be triggered by a variety of noxious particles and gases [2], especially cigarette smoke [81], worsens the destruction of the lung parenchyma and disrupts normal repairment and defense mechanisms, leading to remodeling of peripheral and central airway structures, and eventual gas trapping [2, 79, 81]. During expiration, individuals with COPD have EFL which occurs as a result of a reduced lung elastic recoil along with increased airway resistance [77, 82] (Figure 2.2). The EFL, which reduces the maximum expiratory flow rate at a given lung volume independent of any increased expiratory pressure that is generated to increase that flow is the pathophysiological hallmark of COPD [83, 84]. Aging [85], body position (supine) [86], high ventilatory requirements (especially exercise), hyperpnea, and airflow reduction, have been identified as possible factors that can additionally contribute to a worsening of the EFL [87].

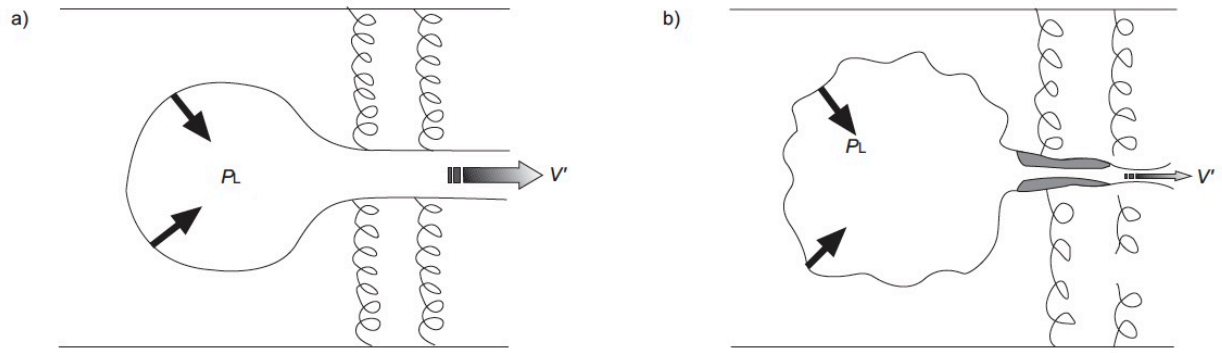

Figure 2.2. Schematic representations of alveolar units.

a) in health and b) in COPD. PL: lung recoil pressure, V': gas flow. By O'Donnell et al. (2006) [82].

2.3.3 Gas Exchange Abnormalities

The destruction and inflammation of the pulmonary structures result in uneven distribution of ventilation in the lungs, causing inefficient alveolar ventilation in individuals with COPD [88, 89]. Gas exchange abnormalities occur from inadequate alveolar ventilation in such individuals [63, 88]. The destruction of alveolar walls leads to a reduction in the surface area available for gas exchange in the lungs [63]. Moreover, loss of the alveolar walls and pulmonary capillaries alters the distribution of alveolar ventilation and pulmonary blood flow [ventilation-perfusion (V/Q) matching] [63, 90]. The resulting V/Q mismatching causes an exaggerated dead space (VD) and has been reported to be an important contributor to the hypoxemia in COPD [63, 90, 91]. There is evidence that the V/Q ratio is dependent on the severity of COPD [63, 90].

2.3.4 Lung Hyperinflation

Lung hyperinflation is an abnormal increase in the volume of air that remains in the lungs at the end of tidal expiration [15, 92]. It implies an elevation of resting FRC above the normal condition [92, 93]. Hyperinflation can be classified into two types: static and dynamic (DH). Static hyperinflation is associated with a reduction in lung elasticity [92, 93]. In normal lungs, the alveoli and airways with proper elasticity enable the airways to open during inspiration and provide a balance between lung recoil and chest wall recoil. However, in COPD, the loss of lung recoil pressure occurs because of destruction of the elastic fibers in the lung parenchyma [93]. As a result, the equilibrium between the inward lung recoil pressure and the outward recoil pressure of the chest wall occurs at a higher FRC. Clinical findings suggest that individuals with COPD may not be negatively affected by hyperinflation until the disease is severe, because of the slow development of the disease and adaptation of the respiratory system [15].

In addition to the static hyperinflation, individuals with COPD can also develop DH independently or in addition to static hyperinflation [93]. DH will be discussed in more detail in Section 2.4.1.

2.4 Exercise Intolerance in COPD

Exercise intolerance signifies an inability to reach physiological standards or sustain the metabolic demands during exercise [94, 95]. Various factors can contribute to the exercise intolerance in individuals with COPD including DH, ventilatory limitation, and skeletal muscle dysfunction [34, 35, 96, 97].

2.4.1 Development of DH During Exercise in COPD

DH is an exercise-induced increase in the end-expiratory lung volume (EELV), i.e. FRC, which occurs secondary to EFL and contributes to limiting exercise capacity in individuals with COPD [75]. In response to the metabolic demands of exercise, healthy individuals increase their VE by first increasing the depth of breathing, followed by an increased respiratory rate (RR) [98]. In healthy lungs, expiratory airflow is unlimited during exercise, which allows a complete expiration before the next inspiration [93]. As shown in Figure 2.3 (a), in healthy individuals, EELV decreases whereas the end-inspiratory lung volume (EILV) increases during exercise which allows the tidal volume (VT) to be increased [75]. In contrast, individuals with COPD tend to predominantly increase RR, and the increased resistance of expiratory airflow prolongs the time required to completely exhale a given inhaled volume [99]. Hence, DH occurs when inspiration begins before having achieved a full expiration, which leads to gas accumulation and retention within the lungs, resulting in an increased EELV (Figure 2.3 (b)) [93, 100]. As exercise workload increases, EELV increases progressively causing a reduction in the IC [93, 99]. The IC can be measured during exercise by having individuals perform IC maneuvers (taking a deep breath from FRC to TLC) to establish the limits for VT expansion [95] and reliably determine DH during exercise [101-104].

DH creates a threshold load at the start of inspiration that the inspiratory muscles need to overcome before inspiratory airflow can be generated [101]. This increases the work of breathing in individuals with COPD [7]. Moreover, hyperinflation causes an expansion of the chest cavity, leading to a downward displacement of the diaphragm, placing the inspiratory muscles in a suboptimal contractile position thereby reducing their force-generating capacity [19, 105, 106].

The altered chest wall geometry also causes a decrease in the diaphragm's area of apposition to the rib cage and a reduced insertional component, limiting the ability of the diaphragm to produce rib cage expansion [19, 107, 108].

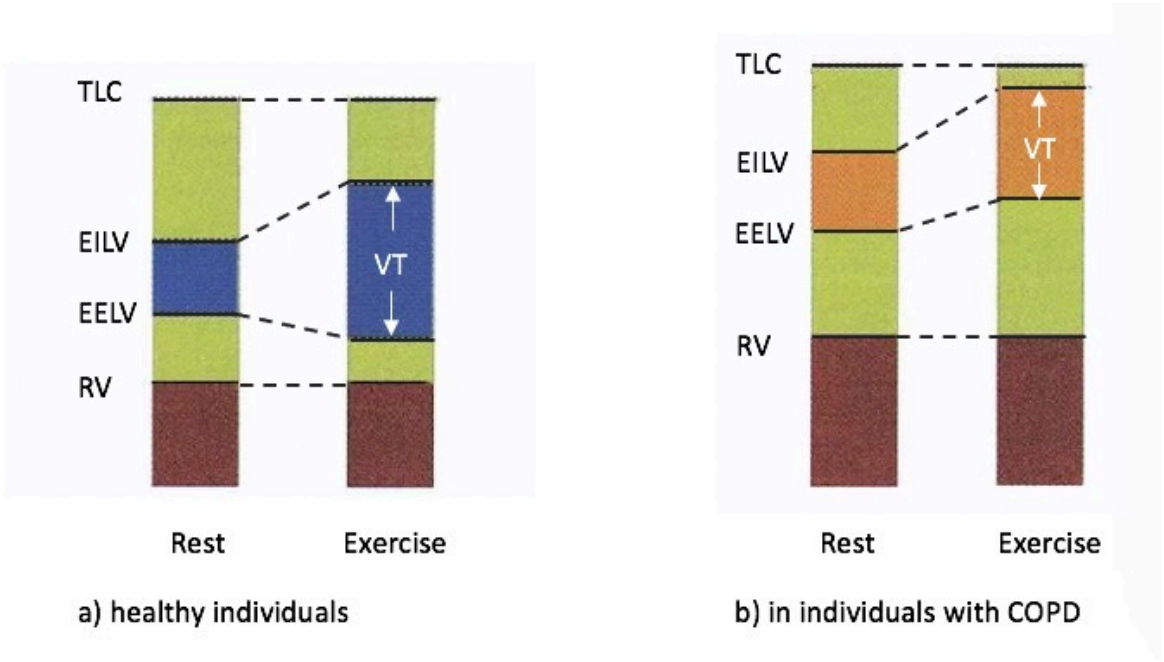

Figure 2.3. Operational lung volumes at rest and during exercise in individuals who are healthy and those with COPD.

TLC: total lung capacity; EILV: end inspiratory lung volume; EELV: end expiratory lung volume; RV: residual volume; VT: tidal volume. Adapted from Cooper., 2006 [75].

2.4.2 Dyspnea on Exertion

Dyspnea, which is the subjective experience of breathlessness, is one of the major cardinal symptoms of COPD [109]. It is often described by patients as an uncomfortable urge to breathe, air hunger, chest tightness, and/or gasping [2, 7]. Dyspnea often becomes more severe as the disease advances [109]. Individuals with COPD initially experience the unpleasant sensation during physical exertion or more demanding physical activities which require increased breathing effort, and in more severe disease, the symptom can appear even during resting breathing [110]. Studies have shown that individuals with COPD often assume a more sedentary

lifestyle in an attempt to avoid the unpleasant sensation of dyspnea [111, 112]. The pathogenesis of dyspnea is complex and multifactorial and the complete physiologic mechanisms are not yet fully understood [82]. Dyspnea can limit exercise capacity [35, 113] and has been shown by a number of studies to be strongly correlated with DH during exercise [15, 17, 18, 82, 114].

In healthy individuals, EILV increases and EELV decreases during exercise, allowing VT expansion to occur on the most linear portion of the respiratory system's sigmoid pressure-volume (P-V) curve (Figure 2.4., a) [82]. Such individuals increase their alveolar ventilation during exercise to cope with the increased metabolic demand [115]. The mechanical response of the respiratory system closely matches the increased neural respiratory drive (i.e., neuromechanical coupling) that occurs during exercise in healthy individuals [101, 116]. In individuals with COPD, VT encroaches on the upper nonlinear extreme of the respiratory system's P-V relationship (Figure 2.4., b) as a result of static and dynamic hyperinflation [82]. Therefore, individuals with COPD mainly increase VE by increasing their RR, contributing to the perception of dyspnea as exercise progresses [15, 117-119]. Moreover, DH also alters the chest wall geometry, which limits the transdiaphragmatic pressure generation capacity, and decreases the zone of the apposition of the diaphragm [19, 77]. As a result, individuals with COPD, particularly those who are hyperinflated, experience a greater neural respiratory drive to support any given VE during exercise compared to healthy individuals [120, 121]. The neural respiratory drive can be measured by quantifying the electromyogram of the diaphragm (EMGdi) [121]. Previous studies have shown that the intensity of dyspnea during exercise in individuals with COPD was correlated with the EMGdi [122, 123]. As a result of abnormal dynamic ventilatory mechanics, individuals with COPD experience a disparity between respiratory effort and the mechanical ventilatory response when performing exercise [15, 82]. The resulting neuromechanical uncoupling of the respiratory system during exercise has been shown to contribute to the perception of exertional dyspnea and exercise intolerance in individuals with COPD [31, 101, 106].

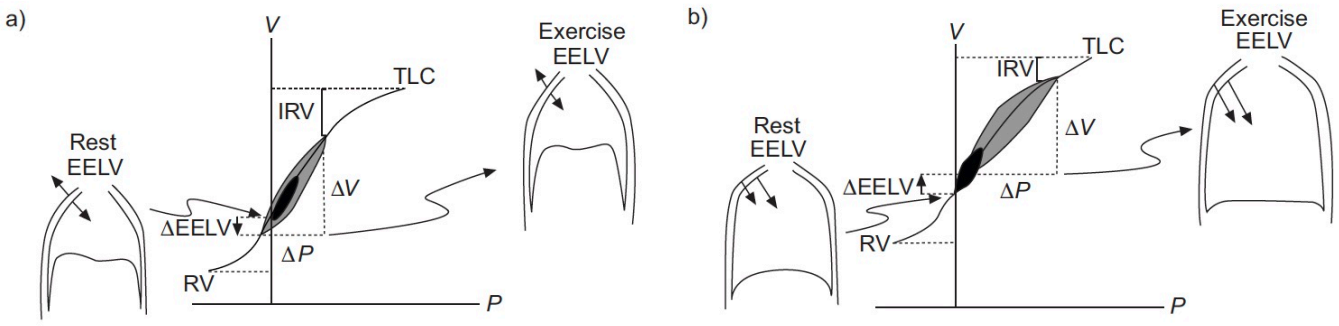

Figure 2.4. Pressure-volume (P-V) relationship of the total respiratory system a) in health and b) in COPD.

EELV: end expiratory lung volume; IRV: inspiratory reserve volume; RV: residual volume; TLC: total lung capacity; ΔP: change in pleural pressure; ΔV, change in volume. By O'Donnell & Laveneziana. (2007) [82].

2.4.3 Skeletal Muscle Dysfunction

Skeletal muscle dysfunction is a common manifestation in COPD, leading to a reduced HRQoL as well as a reduced life expectancy [19, 124, 125]. It is characterised by a decline in both the strength and endurance [111, 126-128] as well as a decrease in the metabolic inefficiency of the affected muscles [129]. Abnormalities in muscle function and structure occur in both the respiratory and peripheral muscle groups and with various contributing factors (Figure 2.5).

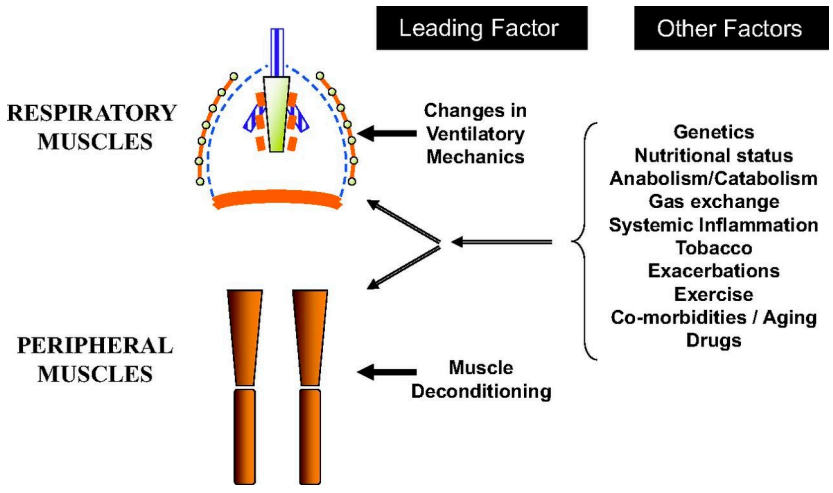

Figure 2.5. Factors that contribute to muscle dysfunction (respiratory and/or peripheral muscles dysfunction) in COPD.

By Gea et al. (2013) [19].

2.4.3.1 Respiratory Muscle Dysfunction

Studies have demonstrated that respiratory muscle function is impaired in individuals with COPD [130-133]. One of the major factors contributing to respiratory muscle dysfunction is the hyperinflation. In COPD, hyperinflation results in a shortening of the inspiratory muscles, causing them to have a less favorable length-tension relationship (particularly of the diaphragm), and reducing their ability to generate pressure [19, 77, 130]. Moreover, altered chest wall geometry reduces the appositional action of the diaphragm, limits the capacity of lower rib cage expansion [107, 130]. As a result, respiratory muscle contraction cannot produce the pressure required to maintain adequate alveolar ventilation, which in turn affects gas exchange [19]. Inefficient gas exchange leads to an increase in work of ventilation, resulting in a reduced supply of oxygen to the respiratory muscles, which contributes to respiratory muscle dysfunction [134]. Other systemic factors such as systematic inflammation, nutritional abnormalities, and therapeutic drugs, etc. (Figure 2.5) also play a role in respiratory muscle dysfunction [19]. In addition, these mechanical and systemic factors may lead to cellular and molecular changes within the muscle, including the increases in mitochondrial density, type I fibers (fatigue-resistant fibers), and myosin heavy chain I in the diaphragm [19, 135, 136].

2.4.3.2 Peripheral Muscle Dysfunction

In addition to respiratory muscle dysfunction, individuals with COPD also exhibit peripheral muscle dysfunction, especially of the lower limbs (i.e., quadriceps) [111, 127, 128, 137, 138]. This is associated with various factors, including fiber type shift (from type I: fatigue-resistant fibers to type II: fatigable fibers) [138-140], muscle atrophy [139], mitochondrial dysfunction [141] and decreased oxidative capacity (a reduced percentage of oxidative fibers with an

increased percentage of glycolytic fibers) [129, 139]. Other factors such as inflammation, malnutrition, oxidative stress and hypoxemia also appear to play a role [139]. Furthermore, peripheral muscle function in COPD shows a large interindividual heterogeneity [139]. Seymour et al. (2010) [127] suggested that the prevalence of lower limb muscle dysfunction tended to be higher in more severe COPD. It should be noted that individuals with COPD often report an increased sensation of leg fatigue during exercise due to peripheral muscle weakness, which has been shown to be a factor in reducing exercise capacity [139, 142, 143]

2.5 Exercise Evaluation in COPD

The assessment of exercise in COPD can provide useful information for individualizing the exercise prescription and instructing the clinical management in order to generate proper intervention and improve current rehabilitation programming [144]. To date, different exercise tests including incremental symptom-limited exercise (on bicycle/treadmill), and functional walking test [such as six-minute walk test (6-MWT), shuttle walk test (SWT)], have been used to quantify the extent of physiological and functional abnormalities in individuals with COPD. Among them, the laboratory-based incremental cycle ergometry test is accepted as the gold standard for assessing exercise capacity, and is widely used in most pulmonary diseases [145]. A cycle ergometry allows measurement of metabolic and physiologic parameters, and provides an accurate quantification of the work rate during exercise [146]. It is easy to achieve with cycle ergometry a linearity between work rate and oxygen uptake (VO_2) responses during exercise [146]. One of the limiting factors of cycle ergometry is its non-relevance as an exercise form relative to real-life, while walking tests are more realistic and better simulate the daily activity [21]. Different treadmill exercise protocols have been used in previous studies [147-150]; however, these protocol designs had a number of inherent limitations 1) the non-linear increase in VO_2 relative to workload; 2) a variability in test duration due to different participant exercise capacities; 3) an inability to set and adjust the initial speed and grade increments according to the individuals' exercise capacities. Therefore, subsequent studies developed treadmill ramp protocols in which simultaneous changes were made to both speed and grade, thereby ensuring an appropriate test duration, and a linear relationship in the VO_2 responses [146, 151]

2.6 Exercise Responses in Individuals with COPD and Healthy Individuals

In all individuals, the metabolic demands of the working muscles increase progressively as exercise intensity increases. In order to meet this increased metabolic demand, healthy individuals increase their alveolar ventilation while maintain a balance between the increased central respiratory drive and the mechanical/muscular response of the respiratory system [101, 152]. Therefore, EELV and IRV decrease, while the EILV increases, which permits expansion of the VT during exercise in healthy individuals [75, 153]. However, peak exercise VE has been shown to be significantly lower in individuals with COPD compared to healthy controls [154]. This decreased ventilation is directly related to the EFL and attendant DH in COPD [93, 100, 154]. In individuals with COPD, EELV progressively increases during exercise, causing the EILV to approach TLC [93, 100]. As exercise progresses, VT becomes constrained, and further increases in VE are mainly accomplished by increasing the RR [15, 117-119]. As a result, individuals with COPD adopt a more rapid and shallow breathing pattern [155]. This tachypnea can lead to further DH which further constrains the VT expansion during exercise, and contributes to increased exertional dyspnea [106]. There is evidence that individuals with COPD typically experience greater dyspnea at any given workload during exercise compared to healthy individuals [12, 13, 156]. Furthermore, VD has been observed to be exaggerated in COPD [89, 145], causing a different pattern of VD/VT ratio during exercise compared to healthy individuals. Typically as breathing deepens during exercise, the ratio of VD/VT decreases as exercise intensity increases in healthy individuals; while it remains at a higher level in individuals with COPD, due to V/Q mismatching during exercise [157].

Exercise capacity is often measured by the duration and/or peak VO_2 achieved during exercise, representing the maximum ability to perform exercise [117, 158, 159]. Individuals with COPD exhibit a reduced exercise capacity due to the pathological changes of respiratory system and systemic effects of the disease [101, 106, 137, 160]. In such individuals, maximal VO_2 has been reported to be significantly lower due to the inability to achieve the same power output compared to healthy age-matched individuals [12, 13, 154, 156]. Despite an increase in dyspnea, the sensation of leg fatigue has been observed to be higher and to occur at a lower work rate in

individuals with COPD compared to healthy controls [154]. Additionally, leg fatigue has been reported to be the dominant exercise limiting symptom in healthy individuals [117, 161].

2.7 Exercise Responses during Walking and Bicycle Exercise in COPD

Previous studies have compared the physiological responses to walking and bicycle exercise in individuals with COPD [21-24, 26, 37, 38, 162, 163]. Shuey et al. (1969) [36] reported that there was no significant difference between treadmill exercise and bicycle exercise for peak VO_2 in mild to moderate COPD, and Mathur et al. (1995) [37] suggested that this finding was consistent with severe COPD. However, in more recent studies, peak VO_2 has been reported to be higher during treadmill exercise compared to bicycle exercise [24, 162, 163]. Furthermore, no gender difference has been observed in the VO_2 response to treadmill and cycling exercise [38].

Comparing the exercise limiting symptoms in the two types of exercise, dyspnea has been reported to be greater in individuals with COPD during walking exercise; whereas such individuals were more likely limited by leg fatigue during cycling exercise [21-24]. Murray et al. (2009) [24] also reported an earlier onset of dyspnea and leg fatigue during cycling exercise compared to walking exercise.

Inconsistent findings were obtained related to peak VE during exercise. Several studies reported no significant difference in peak VE between treadmill and cycling exercise [37, 38, 164]. Palange et al. (2000) also reported a similar VE at peak exercise during SWT and cycling exercise [23]. In contrast, Luxton et al. (2008) reported a higher peak VE during cycling exercise compared to field walking tests (including 6-MWT and SWT) [26]. Moreover, the rate of VE increase during progressive exercise has been shown to be lower for a given VO_2 during incremental treadmill exercise compared to cycling exercise [25]. Additionally, lower values for $P_{ET}CO_2$, VCO_2/VO_2 and VE/VCO_2 have been reported during walking exercise compared to bicycling [22, 23, 25, 26]. Despite similar values for HR [23, 26, 37, 38, 164], oxygen saturation (SpO_2) has been reported to be lower during walking than bicycle exercise [25, 37, 38].

It has been proposed that the potential differences in physiological responses to walking and cycling might be associated with the different muscle masses involved in the two forms of exercise [23, 162]. A smaller muscle mass (i.e., quadriceps) is recruited during bicycle exercise, whereas several muscle groups (i.e., limb muscles and trunk muscles) are said to be involved with walking exercise [23, 162]. Therefore, each muscle fiber is more burdened at a comparable intensity during bicycle exercise compared to walking exercise, leading to greater lactate production [23, 37].

CHAPTER III. EXPERIMENTAL CONDITIONS OF RESTRICTED AIRFLOW LIMITATION

3. STARLING RESISTOR

A SR can be used to generate a constant and restricted airflow limitation in healthy individuals to simulate the restriction experienced by individuals with COPD [30]. The device consists of a collapsible tube inside a rigid chamber that is placed on the expiratory line of a breathing circuit [31]. The chamber is connected by a tube to a valve system on the expiratory side (Figure 3.1). The pressure within the chamber is determined by an adjustable valve to maintain a limited but constant value of the restricted flow regardless of any increasing expiratory pressure that occurs with breathing [30]. In the process of exhalation through the SR, the pressure at the inlet of the collapsible tube becomes greater than the pressure inside the tube, causing it to partially collapse. The more expiratory force is generated, the more collapsed the tube becomes. Therefore, the increased resistance of the collapsible tube prevents an increased expiratory flow, causing a lower pressure at the outlet. Since the pathophysiological effects of the imposed SR are transient, it is safe to use this experimental device to simulate in healthy individuals the EFL that is experienced in COPD without any long-lasting sequelae [30].

Previous studies have used the SR in healthy individuals to evaluate the effects of external EFL (limited to ~0.8-1.0 L/s) during exercise, although typically these studies were carried out using leg cycle ergometry [27-32, 165]. The SR consistently reduced exercise capacity, with values of WLpeak reported to be approximately two-thirds of the control values with no SR (NSR) [27-29]. Studies reported that the intolerable dyspnea at peak exercise was the predominant factor leading to exercise cessation with the SR [30, 31]. Kayser et al. (1997) [31] suggested that DH occurring during exercise with the SR might be an important factor contributing to the observed dyspnea and exercise intolerance. Subsequent studies however reported that the imposed EFL does not necessarily cause DH in all participants, as some individuals remained non-hyperinflated during exercise with the SR [28, 29, 32]. In these individuals, even in the absence of DH, the perception of dyspnea was observed to increase progressively during exercise and was found to be

correlated with the pressure produced by the expiratory muscles in an attempt to overcome the EFL [29, 31]. Participants were also observed to increase their mean inspiratory flow indicating an additional increase in central drive for inspiration during exercise with the external EFL [28, 30]. The SR was also shown to consistently increase $P_{ET}CO_2$ levels during exercise [30, 31], and this was significantly correlated with the expiratory pressure generated [30]. Overall, the SR, appears to reproduce the important clinical features of COPD including intense exertional dyspnea, increased respiratory muscle recruitment, as well as CO_2 retention, which eventually contribute to exercise intolerance in all EFL bicycle exercise [27-32, 165].

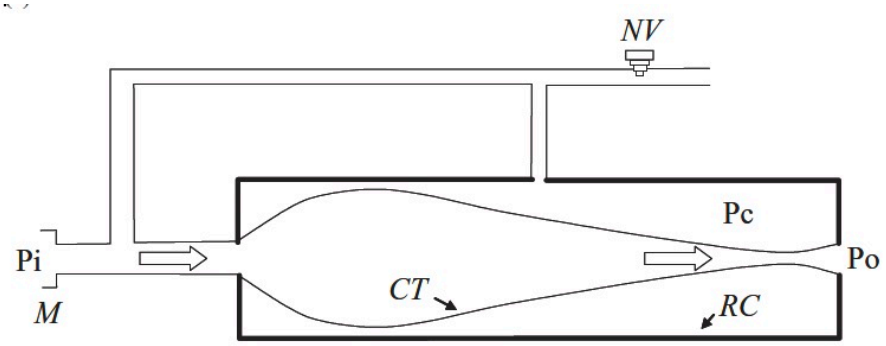

Figure 3.1. A conceptual diagram of a SR.

CT: collapsible tube; RC: a rigid chamber; Pi: pressure at inlet; Pc: pressure inside the chamber; NV: a needle valve; Po: pressure at the outlet. By Alverti et al. (2007) [30]. Flow is driven through the SR from left to right by an applied pressure differences adjusted by the NV.

CHAPTER IV. RATIONALE

EFL is the pathophysiologic hallmark of COPD [4, 5]. Exertional dyspnea and exercise intolerance are the most common symptoms experienced by individuals with COPD [3, 39]. A SR can create an external EFL in healthy individuals in order to simulate the restricted airflow experienced by individuals with COPD [30]. Several studies have previously used this experimental device in healthy individuals and evaluated the pathophysiological responses during exercise on a cycle ergometer [27-32, 165]. In these studies, the SR generated a constantly limited expiratory flow and consistently caused increased exertional dyspnea, exercise intolerance, greater recruitment of respiratory muscles, and an increased $P_{ET}CO_2$ during incremental bicycle exercise [27-32, 165]. The SR, therefore, appears to reproduce the important features and physiological responses observed in individuals with COPD during bicycle exercise. However, previous studies which evaluated the SR were only conducted using cycle ergometry. To date, the acute effect of imposing an external EFL during treadmill exercise has not been evaluated. The application of a SR provides the opportunity to evaluate the effect of external EFL within the same participants on exercise performance and physiological responses in the absence of muscle weakness during an incremental exercise on a treadmill.

CHAPTER V. EFFECT OF EXPIRATORY AIRFLOW LIMITATION ON INCREMENTAL EXERCISE CAPACITY AND BREATHING RESPONSES DURING TREADMILL EXERCISE IN HEALTHY INDIVIDUALS

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Word count: 5856 words

5.1 ABSTRACT

RATIONALE: Individuals with chronic obstructive pulmonary disease (COPD) have expiratory flow limitation (EFL) due to obstruction of the airways. Such individuals typically experience dyspnea on exertion and exercise intolerance. A Starling resistor (SR) can be used to simulate the EFL as occurs in COPD in order to evaluate its effect on exercise capacity. Although the SR has been evaluated during bicycle exercise, no studies have studied its effect during incremental treadmill walking.

OBJECTIVES: The objective of the current study was to evaluate the effect of EFL, created by using a SR, on exercise capacity, metabolic parameters, breathing pattern, and exercise limiting symptoms in healthy participants during incremental treadmill exercise.

METHODS: Healthy non-smoking individuals with no remarkable medical history were recruited in this cross-sectional repeated measures study. Participants performed two randomized incremental symptom-limited treadmill walking tests with and without a SR until exhaustion. Peak exercise workload (WLpeak) was assessed as the maximum exercise workload that was achieved and maintained during the last 30 seconds of exercise. Breathing pattern and metabolic parameters were measured breath-by-breath using a Vmax metabolic cart. Inspiratory capacity (IC) and Borg ratings of dyspnea and leg fatigue were measured every minute during exercise.

RESULTS: Fifteen individuals (4 males, 11 females) aged 27 ± 12 years (mean ± SD) participated in the study. Mean expiratory flow with the SR was 0.5 ± 0.1 L/s (mean ± SD). Compared to treadmill exercise without the SR (no EFL), exercise with the SR resulted in a significantly lower WLpeak, as well as a lower peak minute ventilation, O_2 uptake and CO_2 production ($P < 0.001$ for all). Tidal volume, which increased progressively during exercise with and without the SR, was observed to drop at end-exercise with the SR. The lower tidal volume at higher workloads was associated with an increased respiratory rate and a decreased IC indicating dynamic hyperinflation at end-exercise. Dyspnea was reported as the dominant exercise limiting symptom with the SR, while leg fatigue was the dominant symptom reported in the absence of EFL.

CONCLUSION: During treadmill exercise, EFL resulted in a reduced exercise performance and severe dyspnea as exercise intensity increased. A SR can simulate in healthy individuals the exercise limitations that are typically observed in COPD.

Key words: Exercise, Starling Resistor, Treadmill, Chronic Obstructive Pulmonary Disease.

5.2 INTRODUCTION

COPD is characterized by persistent respiratory symptoms and airflow limitation that is not fully reversible [1, 2]. Individuals with COPD demonstrate a reduced exercise capacity [15, 117] which tends to worsen as the disease progresses [166]. Factors that contribute to a limited exercise performance in such individuals include dynamic hyperinflation (DH), an increased dyspnea sensation resulting from ventilatory limitation [101, 106], as well as heightened leg fatigue and reduced muscle aerobic capacity secondary to peripheral muscle dysfunction [137, 160] which can be further compounded by physical inactivity [167, 168].

Laboratory-based incremental leg ergometer exercise testing is the gold standard for assessing exercise capacity in pulmonary disease [145]. The treadmill walking test may however better reflect activities of daily life [21]. Previous studies have compared the exercise responses to both types of exercise in COPD. Inconsistent findings have been reported for oxygen consumption (VO_2) at peak exercise. Several studies found a similar peak VO_2 for walking and cycling exercise [36, 37], whereas others reported VO_2 to be higher during walking exercise compared to cycling [24, 162, 163]. Peak heart rate (HR) was similar regardless of the exercise type [23, 26, 37, 38, 164]. Physiological parameters including ventilatory equivalents for oxygen (VE/VO_2), end-tidal carbon dioxide ($P_{ET}VO_2$), respiratory exchange ratio (VCO_2/VO_2) and oxygen saturation (SpO_2) were reported to be lower during walking exercise compared to bicycle exercise in individuals with COPD [22, 23, 25, 26]. The difference has been explained by the fact that a larger muscle mass (i.e., limb muscles and trunk muscles) are recruited with walking exercise, whereas the quadriceps are predominantly recruited during cycling exercise [22, 23]. Dyspnea was reported as the dominant exercise limiting symptom during walking exercise in individuals with COPD, in contrast to greater leg fatigue with cycling exercise [21-24].

EFL, as experienced in individuals with COPD, has been simulated in healthy individuals using a Starling resistor (SR) applied to the expiratory phase of breathing [27-32, 165]. A SR consists of

a collapsible tube inside a rigid chamber that is placed on the expiration side of a breathing circuit. Positive pressure generated with expiratory effort acts to partially collapse the tube thereby preventing any increase in expiratory flow [30]. Previous studies which investigated the pathophysiological effects of external EFL during bicycle exercise with the SR showed consistent findings of increased dyspnea, limited exercise performance, increased respiratory muscle recruitment, and carbon dioxide (CO_2) retention [27-32, 165].

To date, no studies have evaluated the physiological effects of breathing through a SR during incremental treadmill exercise in healthy individuals. It remains unknown if a SR can reproduce the increased symptoms and limited exercise performance that is observed in COPD during treadmill walking. Therefore, the purpose of this study was to evaluate the effect of an imposed EFL by application of a SR during incremental treadmill exercise on WLpeak, breathing pattern, metabolic parameters, and exercise limiting symptoms in healthy individuals. We hypothesized that an external EFL would result in a reduced exercise capacity, and a greater dyspnea at a given workload (WL) and produce breathing pattern changes as have previously been reported in individuals with COPD.

5.3 METHODS

5.3.1 Study Population

5.3.1.1 Inclusion Criteria

A convenience sample of fifteen healthy individuals aged 20 to 75 years were included in this study. Participants needed to be able to communicate in either English or French.

5.3.1.2 Exclusion Criteria

Individuals were excluded if they had: 1) any respiratory condition or previous thoracic surgery; 2) a history of smoking; 3) any cardiovascular disease and/or previous cardiac surgery; 4)

neuromuscular or neurodegenerative disease; 5) a musculoskeletal condition involving the lower limbs that could interfere with exercise performance; 6) cognitive impairment or inability to provide informed consent.

5.3.1.3 Recruitment

Participants were recruited through research advertisements that were posted at various public locations in Montreal, and by word of mouth. If potential participants indicated willingness to take part in the study, they were contacted by a research assistant who provided further explanations regarding the study.

Ethics approval was obtained from the Center for Interdisciplinary Research in Rehabilitation in Montreal (CRIR-1397-0319) review board. All eligible participants provided their written informed consent prior to participating in the study.

5.3.2 Study Design

This was a randomized, crossover, exploratory study.

5.3.3 Study Procedure

Participants underwent two symptom-limited incremental treadmill walking tests with and without a SR (Figure 5.1). Prior to the actual exercise testing, demographic, medical, and anthropometric characteristics were determined. Participants underwent pulmonary function testing (FEV1, FVC) by spirometry (MIR Spirobank Spirometer) using standardized procedures according to American Thoracic Society (ATS) guidelines [169].

Participants practiced walking on the treadmill while breathing through a tight-fitting face mask which was connected to the SR (approximately 5 minutes). This enabled participants to be acclimatized to the breathing circuit during treadmill walking. Participants then rested for at least 15 minutes to ensure that HR and breathing pattern parameters returned to the baseline level.

After the break, two symptom-limited incremental exercise tests were performed on a treadmill, one with and the other without a SR, the order of which was randomized across participants. There was a break of at least 20 minutes between the two exercise tests to ensure sufficient time for recovery. Each treadmill test was started with 4 minutes of resting breathing, followed by one-minute of warm-up exercise (treadmill speed was set to 0.5 mph with 1% incline). The treadmill speed and grade were then adjusted according to the treadmill ramp protocol by Porszasz et al. (2003) [146], and by using the equation presented in Appendix 1 [170], in order to achieve a linear increase in work rate and VO_2. A maximum speed of 4 mph was used under the condition of breathing with no SR (NSR), while a maximum speed of 3 mph was performed when breathing through a SR [171].

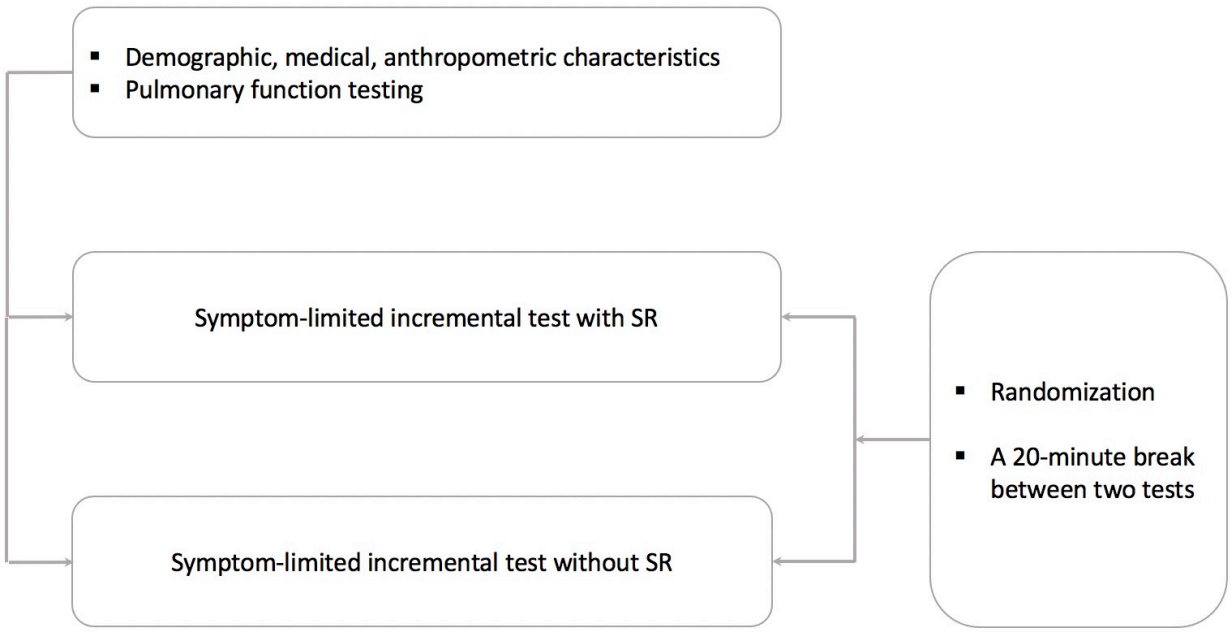


Figure 5.1. Schedule of experimental design.

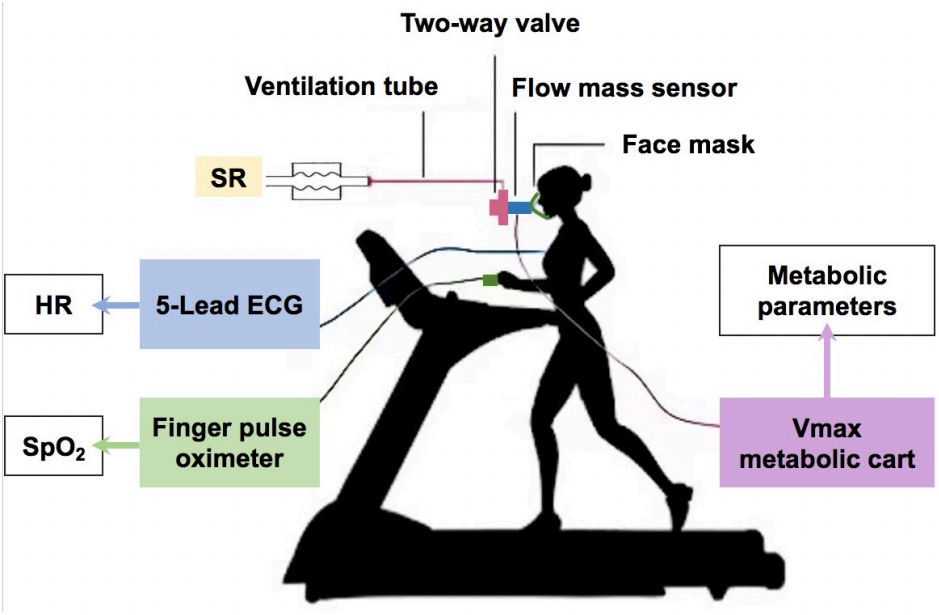
5.3.4 Measurements and Instrumentation

The experimental setup for each participant is shown in Figure 5.2 A.

Maximum exercise capacity was assessed as the peak exercise workload (WLpeak) that was reached and maintained by the participants for at least 30 seconds during the incremental treadmill exercise testing.

Breath-by-breath metabolic parameters [consisting of VO_2, carbon dioxide production (VCO_2), $P_{ET}CO_2$] and breathing pattern parameters (including inspiratory duration (Ti), expiratory duration (Te), total breath duration (Ttot), duty cycle (Ti/Ttot), respiratory rate (RR), minute ventilation (VE), and tidal volume (VT)] were measured continuously during the exercise tests using a Vmax metabolic cart (Vyaire Medical, IL). The recorded data from the Vmax metabolic cart system were exported to a spreadsheet on a portable computer for subsequent analysis. HR and SpO_2 were measured using a 5-lead ECG (GE Healthcare, IL, Vyaire Medical, IL) and finger pulse oximeter (Turner Medical, CT), respectively. Individuals were asked to perform IC maneuvers at rest, every minute during the exercise, and at peak exercise to assess for changes in EELV. Participants were also asked to rate their sensation of dyspnea and corresponding leg fatigue every minute using a modified 10-point Borg Scale (Appendix 2) [172]. Previous studies have shown the Borg scale to be a valid and reliable method for assessing dyspnea during exercise in individuals with COPD, and to also be highly reproducible in healthy individuals [173-175]. During the flow-limited run, a SR (Hans Rudolph, Shawnee, KS; Figure 5.2 B) was applied to the expiratory line of the breathing circuit. The device consisted of a collapsible rubber tube inside a rigid chamber. The pressure difference between the upstream collapsible tube and the chamber determined the maximal expiratory airflow through the resistor, which was set to ~0.5-0.8 L/s . The pressure inside the chamber was adjusted using a controlling dial valve and the expiratory flow was measured using a syringe and independent flow meter,

A)



B) SR

Figure 5.2. Experimental setup for participants.

5.3.5 Statistical Analysis

The collected data were encoded and protected with a password for computer storage. Off-line breath-by-breath analysis was subsequently performed. Descriptive statistics were used to describe the participant characteristics. The values of breathing pattern and metabolic data were averaged every 30 seconds for each participant for the entire exercise test. Group mean values were also calculated from these averaged breath-by-breath data for quiet breathing (QB, last

minute of resting breathing) and peak exercise (last 30 seconds of exercise). Comparisons of the physiological parameters with and without a SR during resting breathing and at peak exercise were carried out using a Student's T-test. To compare exercise with and without the SR, exercise WL was expressed as a percentage of the WLpeak achieved by participants in each of the exercise runs, and subsequently divided into 4 equal segments (0-25%, 25-50%, 50-75% and 75-100% of peak). Group mean values were calculated for each exercise segment. Comparisons of data for each exercise WL segment were carried out using a one-way repeated measure analysis of variance (ANOVA) using the Statistical Package for Social Sciences (IBM SPSS, Inc. Chicago, version 26.0). The level of statistical significance was set to $\alpha = 0.05$. Results were reported as means ± SD unless otherwise indicated.

5.4 RESULTS

5.4.1 Participant Characteristics

Fifteen healthy individuals (4 males, 11 females) aged 27 ± 12 years (mean ± SD) participated in the study. All participants were non-smokers with normal pulmonary function and no remarkable medical history. Anthropometric and baseline characteristics are summarized in Table 5.1.

Effect of SR on peak exercise workload (WLpeak)

Exercise with the SR (with EFL) resulted in a significantly lower WLpeak. The mean WLpeak achieved across participants was 83.1 ± 5.1 and 170.1 ± 10.2 watts ($P < 0.001$), with and without the SR, respectively. The averaged duration of the incremental treadmill exercise test was 6.9 minutes with the SR and 9.8 minutes with NSR.

Effect of SR on breathing pattern

Breathing pattern responses during resting breathing and peak exercise are shown in Table 5.2. There was no difference in the mean inspiratory flow (VT/Ti) at rest, whereas it was significantly lower with the SR compared to NSR at peak exercise. This was mainly due to the lower WLpeak achieved with the SR. As shown in Figure 5.3, the VT/Ti tended to be higher with the SR at all

exercise workloads compared to NSR. The mean expiratory flow (VT/Te) which corresponded to the EFL created by the SR, was significantly reduced at rest and at all exercise workloads including WLpeak compared to NSR (Table 5.2 and Figure 5.3). The expiratory flow was limited to ~0.5 L/s during exercise. Both the Te and the Ttot were significantly prolonged with the SR, resulting in a slower RR, both at rest and especially during exercise (Table 5.2, Figure 5.4 and Figure 5.5). Although the VE was not different with and without the SR at rest, it was significantly reduced with the SR at peak exercise (Table 5.2). As shown in Figure 5.5, VE increased progressively during exercise with NSR, whereas there was little increase with the SR.

The VT was slightly higher at rest and at a given WL during exercise with the SR compared to NSR (Figure 5.4). As can be seen in Figure 5.4 and Figure 5.6, VT increased progressively during exercise with NSR, more than doubling at peak exercise. In contrast, during exercise with the SR, VT was observed to increase initially up to ~ 50% of the WLpeak, after which it declined and was significantly lower compared to NSR at peak exercise (Table 5.2). The drop in VT observed at peak exercise was associated with an increased RR and resulted in a marginal increase in the VE (see Figure 5.5). Additionally, as shown in Figure 5.7, VD/VT decreased progressively as WL increased with NSR. In contrast, with the SR, it was higher at rest compared to NSR ($P = 0.019$), and although it decreased initially, it was observed to increase at higher workloads when the VT began to decline and RR increased. The VD/VT was significantly higher at peak exercise with the SR compared to NSR ($P < 0.001$).

Inspiratory capacity

The IC was similar with or without the SR at rest, whereas it was ~700 ml lower at peak exercise with the SR (Table 5.2). As shown in Figure 5.8, IC was observed to decrease especially at exercise workloads above 50% of WLpeak indicating that individuals experienced progressive hyperinflation at the highest exercise intensities with the SR. However, not all the participants in our study showed the same pattern. Ten participants were observed to hyperinflate during the incremental treadmill walking while five did not hyperinflate throughout the whole of exercise.

Metabolic parameters

Metabolic parameter, including VO2, VCO2 and the PETCO2, were not different with or without the SR during resting breathing (Table 5.2). At peak exercise, VO_2 and VCO_2 were significantly lower when exercise was performed with the SR. As shown in Figure 5.9, a higher $P_{ET}CO_2$ was observed with the application of the SR relative to the same WL with NSR during exercise. The VE and VO_2 as well as the slope of VE/VO_2 relationship were substantially reduced during exercise with the SR (Figure 5.10).

Exertional symptoms

Participants reported no dyspnea with the SR during resting breathing. At peak exercise, dyspnea was similar in the two conditions: 5.6 with the SR and 5.4 with NSR ($P = 0.655$). However, peak dyspnea was reached much faster and at a lower WL during exercise with the SR compared to NSR (Figure 5.11). Leg fatigue at peak exercise with the SR was 2.7 and it was 6.0 with NSR ($P < 0.001$). At end exercise with the SR, 85% of the participants reported that they stopped exercise due to dyspnea, whereas 15% stopped because of leg fatigue. Leg fatigue, however, was the dominant symptom reported with NSR, with 45% of the participants stopping exercise due to leg fatigue, 22% due to dyspnea and 33% due to both.

Cardiovascular parameters

As shown in Table 5.2, SpO_2 was not altered by the SR at rest and peak exercise. As shown in Figure 5.12, we observed a lower SpO_2 during exercise with the SR compared to NSR at comparable workloads. HR, however, was significantly lower with the SR compared to NSR at peak exercise. Considering the fact of the lower WLpeak achieved with the SR, HR was observed to be similar with the EFL relative to the same WL with NSR (Figure 5.12).

5.5 DISCUSSION

This exploratory study evaluated the effect of an imposed EFL by the application of a SR on exercise endurance, breathing pattern, metabolic parameters, and exercise limiting symptoms in healthy individuals during treadmill walking exercise. The main findings were that the imposed EFL that was generated by the SR significantly reduced exercise capacity and increased

exertional dyspnea in the participants during incremental treadmill exercise. The EFL created by the SR decreased VT/Te and resulted in an inability to increase VT at higher exercise levels, promoting a more rapid and shallow breathing and DH at end-exercise. The observed exercise effects were consistent with prior studies conducted using a SR during bicycle ergometry exercise [27-31]. The SR also reproduced, in the healthy individuals, the exercise limitation, DH and increased symptoms typically observed to limit exercise in COPD [2, 33, 118].

The grade and speed of the incremental treadmill exercise in this study were based on a treadmill ramp protocol described by Porszasz et al. (2003) [146] in order to obtain a linear increase in VO_2 in participants. This exercise protocol has been used in previous studies which evaluated exercise responses during treadmill exercise both in healthy individuals and patients with COPD [38, 154, 162]. In the current study, the VO_2 response to the incremental treadmill exercise was linear with and without a SR.

Previous studies, which looked at the exercise responses in healthy individuals breathing with a SR during bicycle exercise, reported a significant lowering of the WLpeak compared to exercise with NSR [28-32]. Aliverti et al. (2005) [27] also reported a lower VO_2 when EFL was created using a SR during bicycle exercise. The values of WLpeak with the SR were approximately 60-65% of the WLpeak with NSR [27-29]. Our data showed that the mean WLpeak was likewise significantly decreased with the SR during treadmill exercise, but the decline corresponded to approximately 49% of the NSR WLpeak. One possible reason for the greater exercise limitation that we observed compared to previous studies might be the larger EFL that was generated by the SR in the current study. The imposed expiratory flow was approximately ~0.5 L/s in our study compared to 0.8-1.0 L/s which was reported in previous studies conducted with bicycle ergometry [27-29].

Without the SR during incremental treadmill exercise in our study, VT, RR and VE were observed to increase progressively with work rate. The increased RR was achieved by increasing the inspiratory and expiratory airflows and shortening both the Ti and Te components of the Ttot, which resulted in little overall change in Ti/Ttot. In contrast, the imposed SR produced an EFL which prevented any increase in the VT/Te and caused the Te and Ttot to be lengthened and

Ti/Ttot to be progressively reduced. Participants initially increased their VT during exercise with the SR by increasing the VT/Ti; however, the average VT was observed to decline and the RR increased at workloads greater than ~50-75% WLpeak. These breathing pattern findings were consistent with the results of previous studies which were obtained using bicycle ergometry [28, 31, 32]. Like our study, others have reported that the VT with the SR was initially greater than with NSR, and that it increased during exercise and subsequently fell at ~75% of WLpeak [29, 31]. These same studies also found that the RR was lower with the SR at the start of exercise and increased as exercise intensity increased [29, 31]. Aliverti et al. (2005) [27] reported that imposing an EFL caused the Ti/Ttot to decrease during bicycle exercise, and the mean values at peak work rate were around 0.25 and 0.44 with and without a SR, respectively. In our data, the Ti/Ttot at peak during the treadmill exercise was 0.25 with a SR and 0.45 with NSR at a comparable WL. Other studies have likewise reported a progressive decline in the Ti/Ttot with the SR during bicycle exercise [29, 31]. A shortening of the Ti/Ttot reduces the burden on the expiratory muscles in the face of an EFL, but does this at the expense of the inspiratory muscles which are required to increase their activation when contracting at a greater velocity of shortening in order to increase the VT in a shortened Ti [27]. The higher VT/Ti with the SR at a given WL compared to NSR indicated a higher central respiratory drive which could have contributed to an increased dyspnea sensation during exercise with the SR.

The faster and more shallow breathing pattern that occurred with the SR during treadmill exercise in our study was associated with a progressive reduction in the average IC at higher exercise work rates, indicating that DH had occurred. DH was also observed at end-exercise with the SR during bicycle exercise in previous studies [28, 29, 31]. The mean IC decreased by ~850 ml with the SR during bicycle exercise [29] compared to 700 ml during treadmill exercise in the current study. In line with previous results [29, 32] we likewise found that not all our participants hyperinflated with the SR during treadmill exercise (five of the fifteen participants were non-hyperinflators). Unlike the previous studies, we found that five non-hyperinflators reached a significantly higher WLpeak compared to the hyperinflators (100 ± 17 watts and 75 ± 16 watts, respectively; $P = 0.013$), although the average dyspnea at peak exercise was identical in both groups (5.6 ± 0.9 and 5.6 ± 1.8, respectively). Although some studies have suggested that the hyperinflation that results with the SR applied during exercise may contribute to exercise

impairment and dyspnea [31], others have maintained that the role of DH in contributing to exercise limitation and dyspnea in individuals who hyperinflate with a SR may be overstated [28, 29, 32]. There is evidence that lung hyperinflation contributes to dyspnea and exercise intolerance in COPD by reducing neuromechanical coupling of the respiratory system and reducing the mechanical efficiency of the shortened inspiratory muscles [35]. However, reportedly about 15-20% of individuals with moderate to severe COPD do not consistently hyperinflate, but still experience exercise intolerance and have higher exertional dyspnea ratings [99]. Differences in how hyperinflation is measured has been suggested to have contributed in part to the contradictory results obtained [99]. However, the proportion of patients who have DH during exercise increases with increased severity of airflow limitation in COPD [176].

There is evidence that externally imposed expiratory resistive loads can contribute to breathing difficulty in healthy individuals [16]. Kayser et al. (1997) [31] reported that breathlessness was the dominant symptom that caused healthy participants to stop exercising when breathing with a SR during leg cycling. In the same study, the investigators suggested that the increased expiratory pressure that is needed to overcome the resistance of the SR might play an important role in contributing to dyspnea during EFL bicycle exercise [31]. Aliverti et al. (2007) [30] reported that the mean dyspnea measured with a modified Borg scale at WLpeak during incremental bicycle exercise with the SR was around 9.0-10.0, but was significantly lower (~5.0) with NSR. Similar ratings with the SR during leg cycling have been reported by others [29, 32]. In contrast, our data showed that the perceived dyspnea was similar at peak exercise for both the SR and NSR groups (5.6 versus 5.4, respectively), although ratings were higher for any give work rate with the SR. Also, leg fatigue at peak exercise was significantly lower with the SR compared to NSR (6.0 versus 2.7, respectively). Moreover, about 85% of our participants reported that they stopped EFL treadmill exercise due to dyspnea compared to 45% in the NSR group. Our results are consistent with previous studies which reported that individuals with COPD exhibited earlier increases in dyspnea sensation at lower exercise workloads compared to healthy controls but experienced similar levels of dyspnea at peak exercise during leg cycling [17, 177] and treadmill exercise [154]. Several studies have also found that individuals with COPD perceive greater dyspnea with walking compared to leg cycling and greater leg fatigue with cycling [21-24]. Individuals who terminate exercise because of breathing discomfort have been

shown to have greater airflow limitation and mechanical constraints to ventilation compared to healthy controls [154]. Studies which imposed the SR during leg cycling also found larger gastric, pleural and transdiaphragmatic pressures during breathing indicating a greater recruitment of the expiratory muscles to overcome the EFL, and of the inspiratory muscles because of the inspiratory flow increase [28, 29, 31]. Preliminary regression analyses by Iandelli et al. (2002) [29] suggested that these high respiratory muscle pressures were major factors contributing to the severe dyspnea and exercise limitation that was experienced with the SR. Different from our study, treadmill exercise in individuals with mild to moderate COPD was shown to result in higher levels of leg discomfort [154]. Given that previous studies of the SR during leg cycling did not evaluate leg discomfort, we are unable to confirm our findings. However, individuals with COPD can have peripheral muscle weakness [19], which could contribute to leg discomfort and increase dyspnea during exercise [97, 131]. This is one of the limitations of the SR model of COPD.

Despite the increased breathlessness, leg fatigue has also been shown to provide important feedback in limiting central output and reducing peripheral muscle oxidative capacity [142, 178, 179], which could contribute to the exercise intolerance in both healthy participants and individuals with COPD [179, 180].

The imposed EFL in our study led to an increased $P_{ET}CO_2$ especially at exercise levels where the IC was seen to decline after ~50% of WLpeak. This was associated with a more rapid and shallow breathing pattern and an increased VD/VT, indicating a likely decreased alveolar ventilation. An elevated $P_{ET}CO_2$ was a consistent finding in previous studies where the SR was used during bicycle exercise [27-31]. Unlike these studies, however, the average $P_{ET}CO_2$ in our study rose above 45 mmHg only in six of the study participants. An elevated $P_{ET}CO_2$ could potentially stimulate neural drive and contribute to an increased dyspnea sensation and poor exercise performance [30]. The $P_{ET}CO_2$ was previously found to be correlated with the expiratory pressures generated with the SR [30]. Given that the SR decreases Ti/Ttot during exercise, i.e. more time is spent in expiration, it has been suggested that the SR might decrease the venous return, reduce pulmonary capillary blood volume and thereby increase alveolar VD [30].

Individuals in our study were not found to desaturate significantly more with the SR during treadmill exercise, however, the SpO_2 was lower at any given WL with the SR.

5.6 STUDY LIMITATIONS

There are some limitations inherent in our study. First, this was an explanatory pilot study with a small sample size (15 participants). Further studies with a larger sample size can contribute to more generalizable outcomes. Secondly, the experimental condition that is generated by the SR is abrupt and non-permanent, while the development of symptoms in individuals with COPD is slow. Likewise, the SR cannot recreate the specific pathophysiological characteristics of COPD which include an altered lung or chest wall compliance, remodelling of the airways, destruction of the pulmonary capillary beds, inflammation of the airways and lungs, and abnormalities of chest wall motion. Individuals with COPD also show different extents of observed symptoms and varying severity of the disease. Finally, our healthy participants did not have any muscle weakness, whereas individuals with COPD can have peripheral muscle weakness [19], which could contribute to leg discomfort and an increased dyspnea during exercise [97, 131].

5.7 CONCLUSIONS

Overall, in this study, we demonstrated the EFL created with a SR, resulted in a reduced exercise capacity and increased dyspnea as WL increased during treadmill incremental exercise. To the best of our knowledge, this is the first study to show the impact of external EFL on exercise performance, metabolic parameters, breathing pattern, dyspnea and leg fatigue during treadmill walking exercise with the application of a SR. Our findings for exercise on a treadmill were consistent with the previous findings on exercise responses during bicycle exercise with the application of a SR. The SR can simulate in healthy individuals the exercise limitations and some physiological abnormalities observed in COPD during incremental treadmill exercise.

5.8 ACKNOWLEDGEMENTS

This study was supported by the Center for Interdisciplinary Research in Rehabilitation in Montreal and by the Jewish Rehabilitation Hospital. The authors would also like to thank all participants for their participation in this study.

Table and Figures

Table 5.1. Anthropometric and baseline characteristics.

Variable	Mean ± SD or N (%)
Age, years	26.8 7 ± 12.21
Male, N (%)	4 (26.67)
Female, N (%)	11 (73.33)
Height, cm	167.33 ± 9.42
Weight, lb	144.17 ± 23.49
BMI, kg/m^2	23.33 ± 2.77
FEV_1, L (% predicted)	3.57 ± 0.75 (104.44 ± 14.67)
FVC, L (% predicted)	4.34 ± 0.94 (101.19 ± 15.01)
FEV_1/FVC, %	82.97 ± 5.67

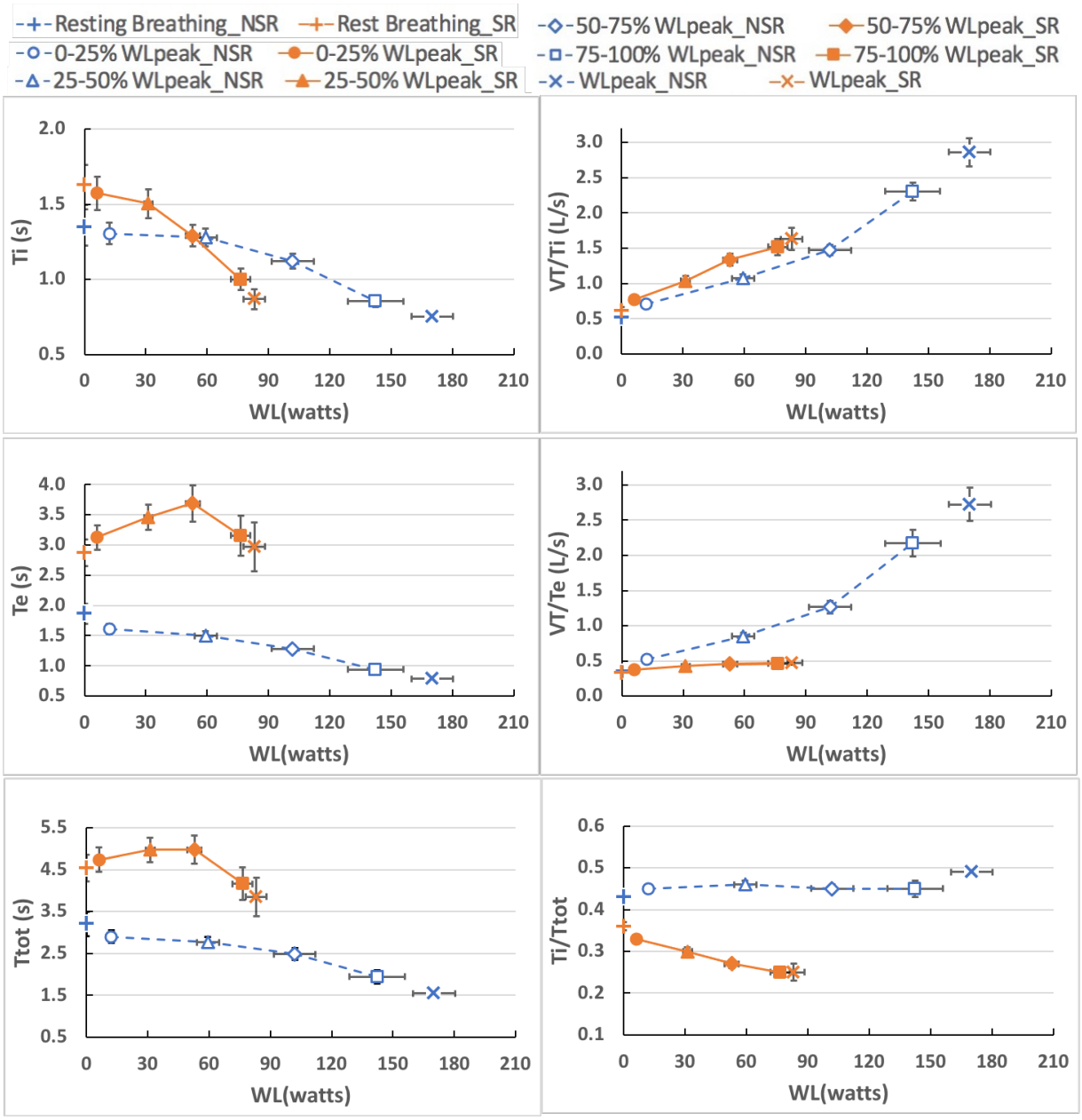
Values are means ± SD. Definitions of abbreviations: BMI, body mass index; FEV_1, forced expiratory volume in 1st second; FVC, forced vital capacity; N, number.

Table 5.2 Physiological parameters at rest and at peak during incremental treadmill exercise in participants.

	Resting Breathing			Peak Exercise		
Variable	NSR	SR	P	NSR	SR	P
Ti, s	1.4 ± 0.1	1.6 ± 0.3	P = 0.197	0.8 ± 0.1	0.9 ± 0.3	P = 0.055
Te, s	2.0 ± 0.5	2.8 ± 0.9	P < 0.001	0.8 ± 0.2	3.0 ± 1.5	P < 0.001
Ttot, s	3.4 ± 0.0	4.5 ± 1.2	P = 0.001	1.5 ± 0.3	3.9 ± 1.8	P < 0.001
VT/Ti, L/s	0.5 ± 0.1	0.6 ± 0.2	P = 0.112	3.0 ± 0.6	1.6 ± 0.6	P < 0.001
VT/Te, L/s	0.4 ± 0.1	0.3 ± 0.1	P = 0.012	2.9 ± 0.7	0.5 ± 0.1	P < 0.001
Ti/Ttot	0.4 ± 0.1	0.4 ± 0.1	P = 0.002	0.5 ± 0.1	0.2 ± 0.1	P < 0.001
VT, L	0.8 ± 0.3	1.0 ± 0.4	P = 0.024	2.3 ± 0.6	1.4 ± 0.7	P < 0.001
RR, bpm	18.9 ± 4.9	14.3 ± 3.3	P = 0.001	40.3 ± 7.0	20.0 ± 10.5	P < 0.001
VE, L/min	13.3 ± 2.4	12.5 ± 3.0	P = 0.239	88.4 ± 19.4	21.1 ± 4.2	P < 0.001
IC, L	2.5 ± 0.8	2.7 ± 0.9	P = 0.636	2.8 ± 0.9	2.1 ± 0.9	P = 0.005
$P_{ET}CO_2$, mmHg	32.8 ± 1.9	31.2 ± 3.4	P = 0.094	41.1 ± 3.4	44.9 ± 5.8	P = 0.016
VO_2, L/min	0.3 ± 0.1	0.3 ± 0.1	P = 0.762	2.8 ± 0.7	1.1 ± 0.8	P < 0.001
VCO_2, L/min	0.3 ± 0.1	0.3 ± 0.1	P = 0.318	3.3 ± 0.8	0.8 ± 0.3	P < 0.001
HR, bpm	83.0 ± 15.7	92.2 ± 15.2	P < 0.333	172.7 ± 11.3	139.1 ± 23.3	P < 0.001
SpO_2, %	97.0 ± 2.3	97.0 ± 1.8	P = 0.316	94.5 ± 2.3	93.7 ± 2.5	P = 0.343

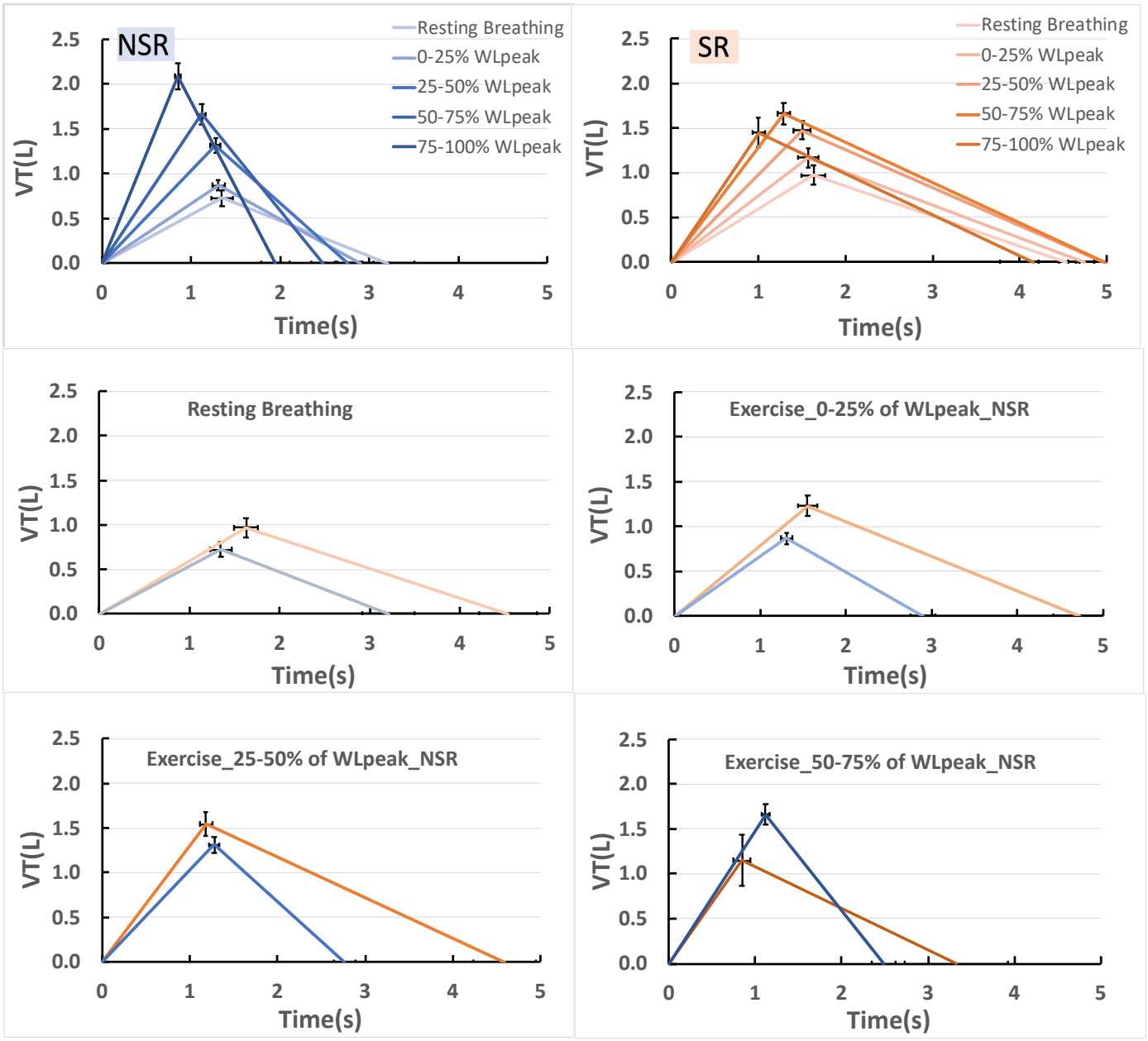
Values are means ± SD. Definitions of abbreviations: SR: with a Starling resistor; NSR: without a Starling resistor, Ti, inspiratory time; Te, expiratory time; Ttot, total breath time; VT/Ti, mean inspiratory flow; VT/Te, mean expiratory flow; Ti/Ttot, duty cycle; VT, tidal volume; RR, respiratory rate; VE, minute ventilation; IC, inspiratory capacity; $P_{ET}CO_2$, end tidal CO_2; VO_2, oxygen uptake; VCO_2, carbon dioxide output; HR, heart rate; SpO_2, arterial oxygen saturation. P < 0.005 is considered statistically significant.

Figure 5.3. Breathing time (Ti, Te, and Ttot), inspiratory flow (VT/Ti), expiratory flow (VT/Te) and duty cycle (Ti/Ttot) during incremental treadmill exercise with and without the SR.



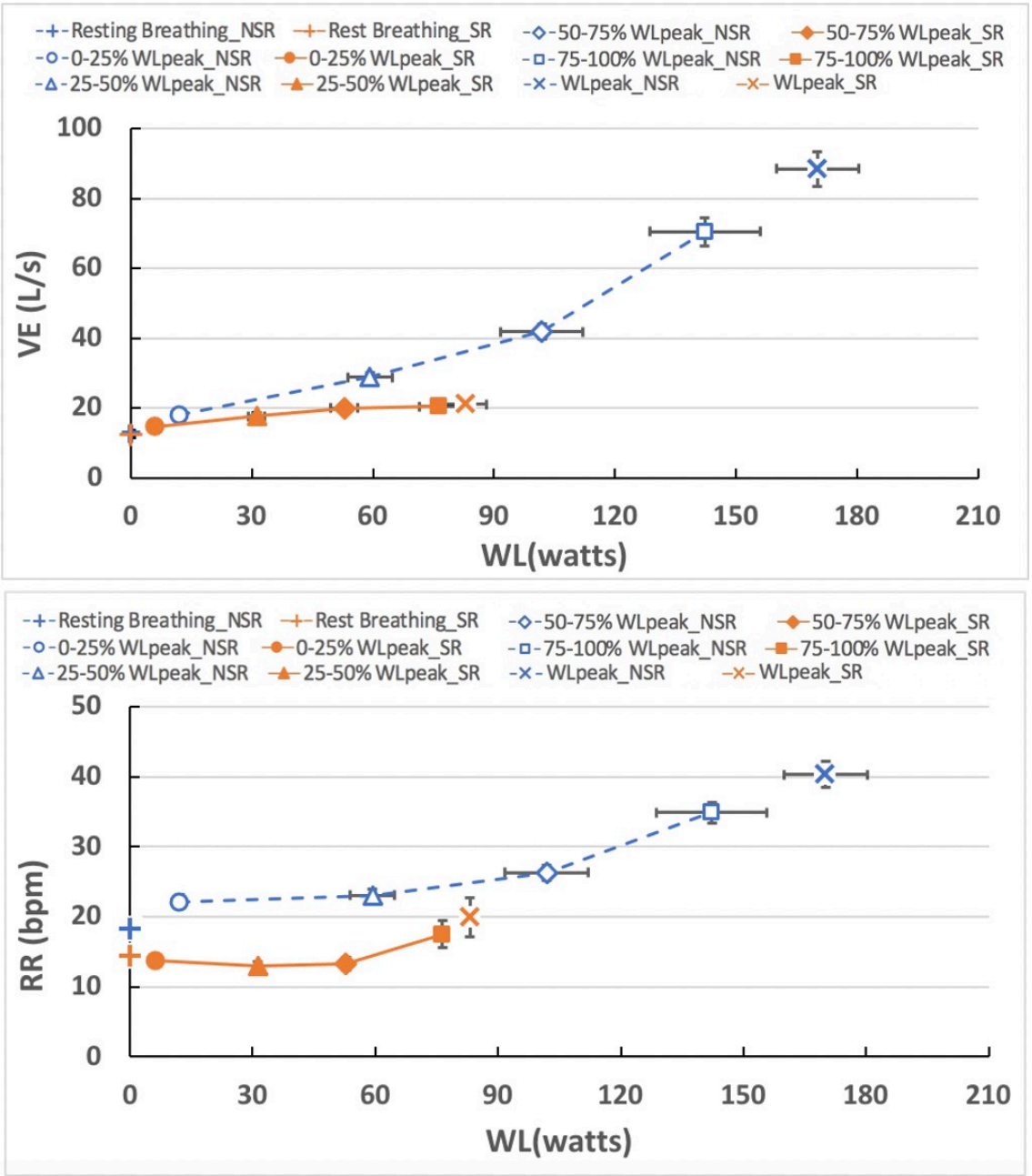
Breathing pattern parameters are shown plotted against exercise workload at rest, at peak exercise and at relative exercise workloads corresponding to 0-25%, 25-50%, 50-75% and 75-100% WLpeak. In the graph, SR: solid lines and orange symbols; NSR: dashed lines and blue symbols. Definitions of abbreviations: Ti, inspiratory time; Te, expiratory time; Ttot, total time; VT/Ti, inspiratory flow; VT/Te, expiratory flow; Ti/Ttot, duty cycle; WL: workload; SR: Starling resistor; NSR: no Starling resistor. Values are means ± SE.

Figure 5.4. Spirograms at rest, during incremental treadmill exercise with and without the SR.



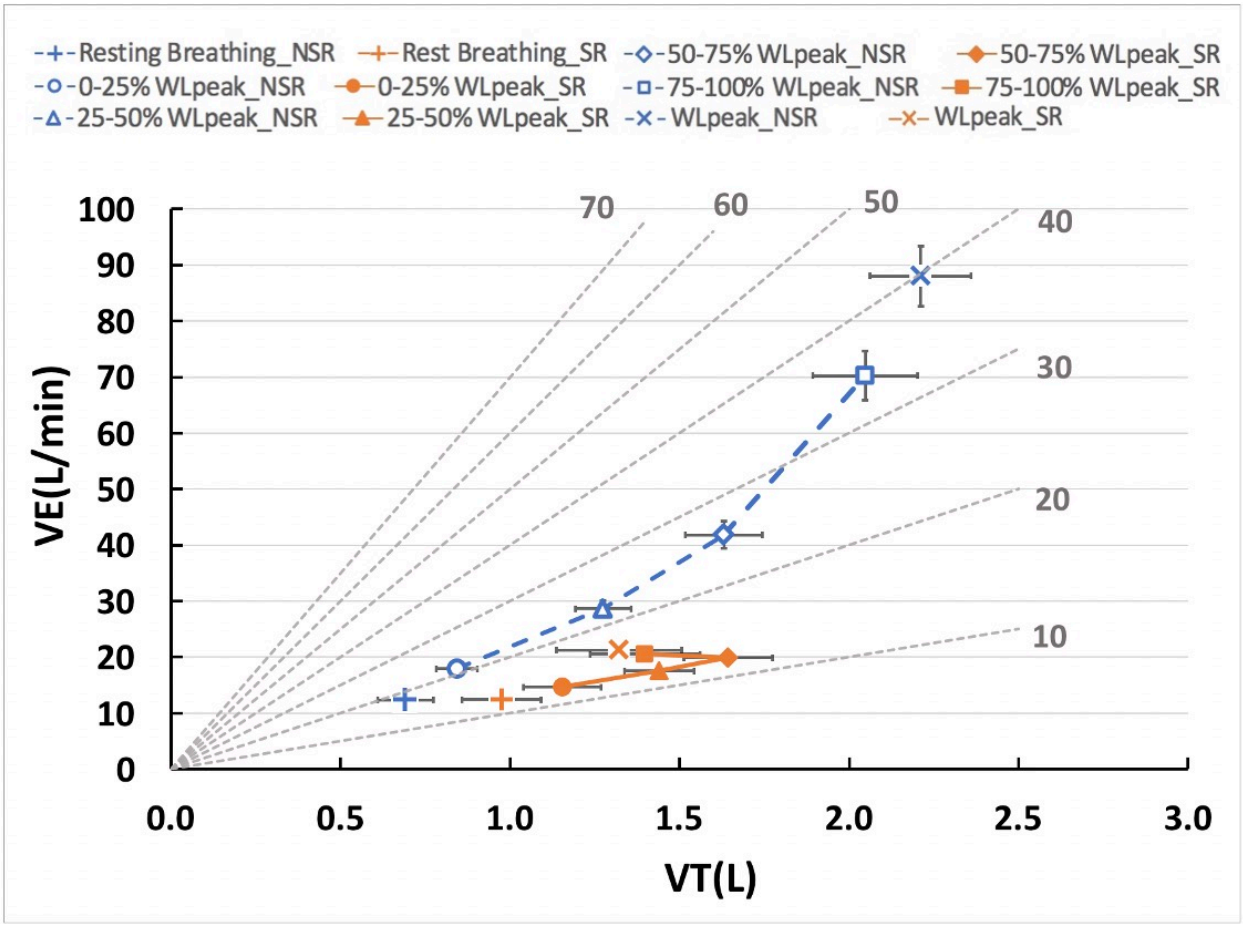
Spirograms are shown plotted for different relative exercise workloads, with and without the SR in the top two graphs and comparing SR and NSR in the remaining graphs. SR: orange lines; NSR: blue lines. Definitions of abbreviations: VT: tidal volume; WLpeak: peak workload; SR: Starling resistor.; NSR: no Starling resistor. Values are means ± SE.

Figure 5.5. Minute ventilation (VE) and respiratory rate (RR) during incremental treadmill exercise with and without the SR.



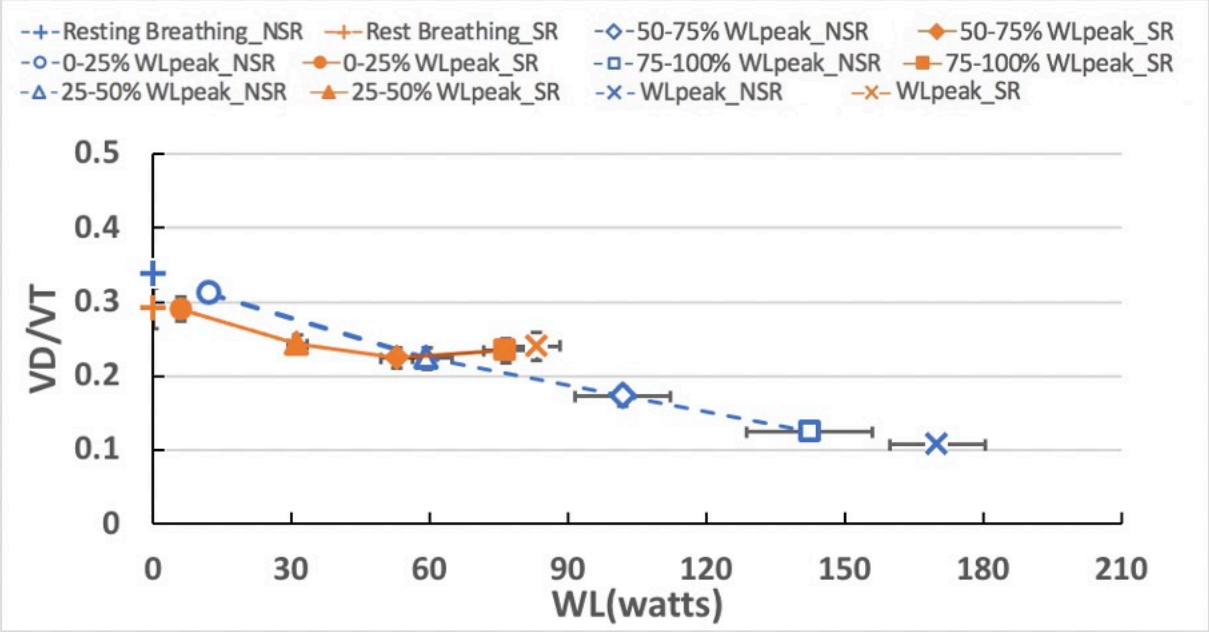
Minute ventilation (VE) and respiratory rate (RR) are shown plotted against exercise workload at rest, at peak exercise and at relative exercise workloads corresponding to 0-25%, 25-50%, 50-75% and 75-100% WLpeak. In the graph, SR: solid lines and orange symbols; NSR: dashed lines and blue symbols. Definitions of abbreviations: SR: Starling resistor; NSR: no Starling resistor. Values are means ± SE.

Figure 5.6. Plot of minute ventilation (VE) versus tidal volume (VT) at rest, during incremental treadmill exercise and at peak exercise with and without the SR.



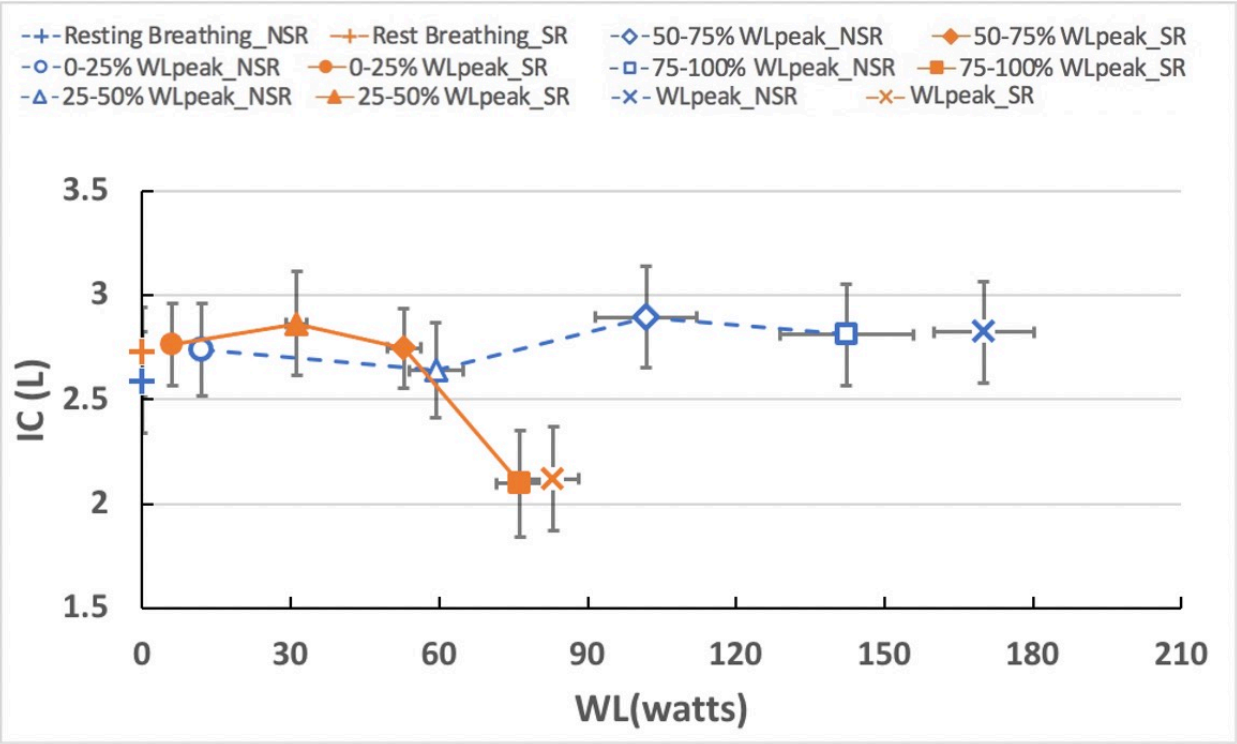
Minute ventilation (VE) is shown plotted against tidal volume (VT) at rest, at peak exercise and at relative exercise workloads corresponding to 0-25%, 25-50%, 50-75% and 75-100% WLpeak. In the graph, SR: solid lines and orange symbols; NSR: dashed lines and blue symbols. Dotted grey lines are isopleths indicating breathing frequency (min^{-1}). Definitions of abbreviations: VE: minute ventilation; VT: tidal volume; SR: Starling resistor; NSR: no Starling resistor. Values are means ± SE.

Figure 5.7. Plot of the VD/VT at rest, during incremental treadmill exercise and at peak exercise with and without the SR.



Graph shows the ratio of dead space ventilation to tidal ventilation (VD/VT) at rest, at peak exercise and at relative exercise workloads corresponding to 0-25%, 25-50%, 50-75% and 75-100% WLpeak. In the graph, SR: solid lines and orange symbols; NSR: dashed lines and blue symbols. Definitions of abbreviations: WL: workload; SR: Starling resistor; NSR: no Starling resistor. Values are means ± SE.

Figure 5.8. Inspiratory capacity (IC) at rest, during incremental treadmill exercise and at peak exercise with and without the SR.



Plot illustrates the inspiratory capacity (IC) at rest, at peak exercise and at relative exercise workloads corresponding to 0-25%, 25-50%, 50-75% and 75-100% WLpeak. In the graph, the averaged values were calculated for 14 participants due to missing data in 1 participant. SR: solid lines and orange symbols; NSR: dashed lines and blue symbols. Definitions of abbreviations: WL: workload; SR: Starling resistor; NSR: no Starling resistor. Values are means ± SE.

Figure 5.9. End-tidal carbon dioxide ($P_{ET}CO_2$) at rest, during incremental treadmill exercise, and at peak exercise with and without the SR.

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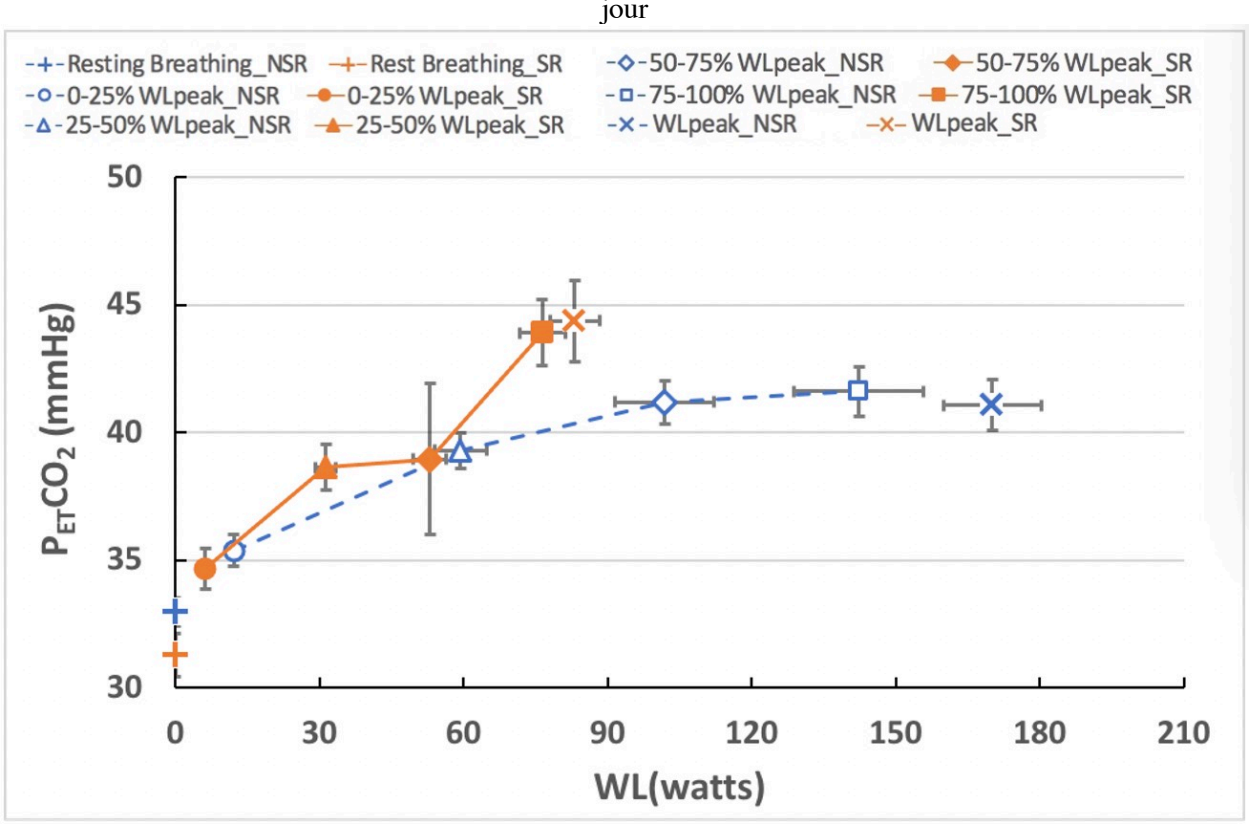
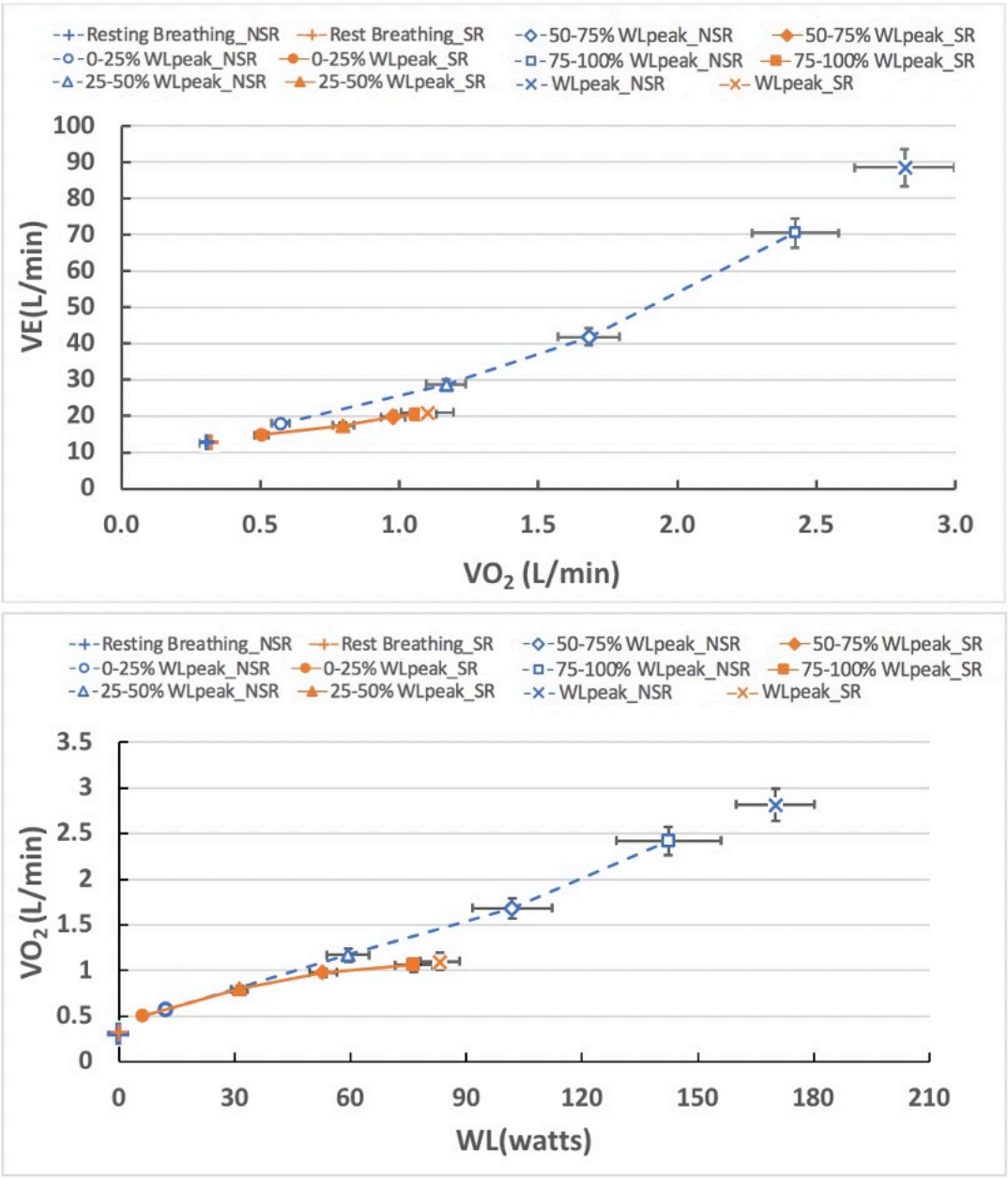


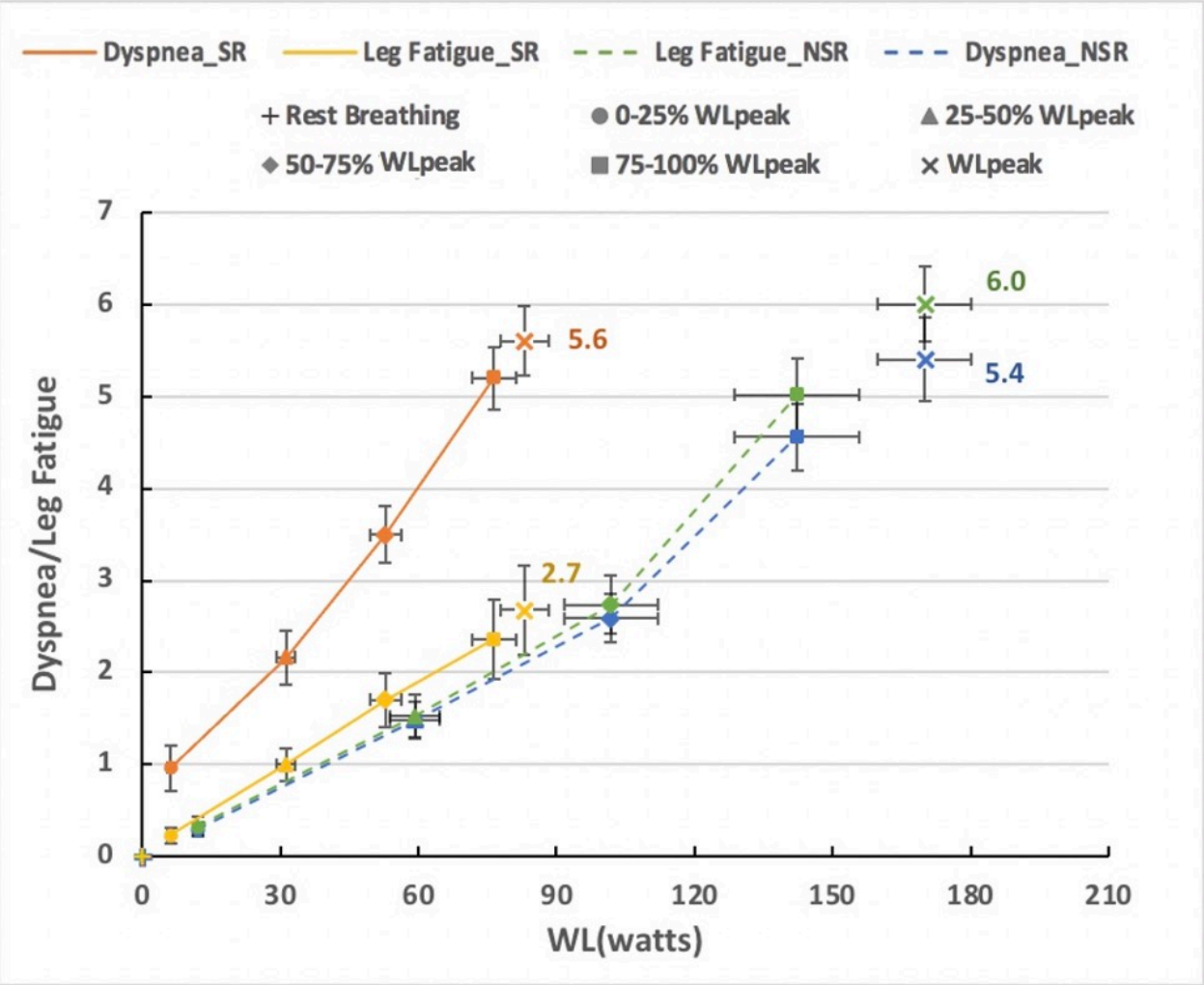
The end-tidal CO2 is shown at rest, at peak exercise and at relative exercise workloads corresponding to 0-25%, 25-50%, 50-75% and 75-100% WLpeak. In the graph, SR: solid lines and orange symbols; NSR: dashed lines and blue symbols. Definitions of abbreviations: $P_{ET}CO_2$: end-tidal CO_2; WL: workload; SR: Starling resistor; NSR: no Starling resistor. Values are means ± SE.

Figure 5.10. Relationship between minute ventilation (VE) and oxygen uptake (VO_2), and VO_2 versus workload at rest, during incremental treadmill exercise and at peak exercise with and without the SR.



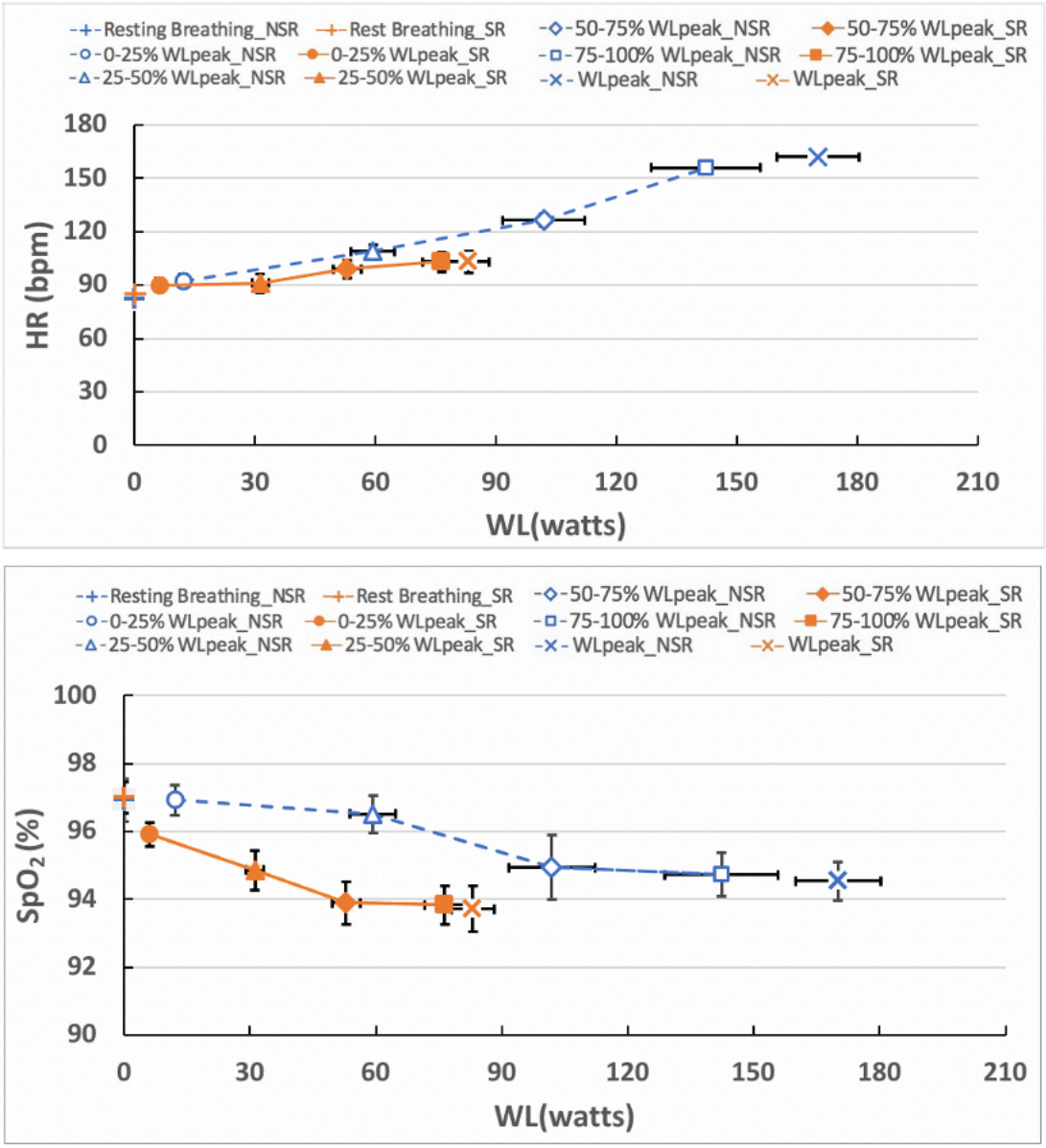
Values are presented at rest, at peak exercise and at relative exercise workloads corresponding to 0-25%, 25-50%, 50-75% and 75-100% WLpeak. In graph, SR: solid lines and orange symbols; NSR: dashed lines and blue symbolsDefinitions of abbreviations: VE: minute ventilation; VO_2: oxygen uptake; WL: workload; SR: Starling resistor; NSR: no Starling resistor. Values are means ± SE.

Figure 5.11. Leg fatigue and dyspnea reported by participants at rest, during incremental treadmill exercise and at peak exercise with and without the SR.



Values are presented at rest, at peak exercise and at the relative exercise workloads corresponding to 0-25%, 25-50%, 50-75% and 75-100% WLpeak. In the graph, SR: solid lines; NSR: dashed lines. Definitions of abbreviations: WL: workload; SR: Starling resistor; NSR: no Starling resistor. Values are means ± SE.

Figure 5.12. Heart rate (HR) and oxygen saturation (SpO_2) at rest, during incremental treadmill exercise and at peak exercise with and without the SR.



Values are presented at rest, at peak exercise and at the relative exercise workloads corresponding to 0-25%, 25-50%, 50-75% and 75-100% WLpeak. In the graph, SR: solid lines and orange symbols; NSR: dashed lines and blue symbols. Definitions of abbreviations: HR: heart rate; SpO_2: oxygen saturation; WL: workload; SR: Starling resistor; NSR: no Starling resistor. Values are means ± SE.

CHAPTER VI: CONCLUSION

This study was conducted during the COVID-19 pandemic. The data that was analyzed involved the first component of a study which looked at the effect of arm loading on walking endurance and breathing patterns in healthy individuals with the application of a SR (titled "*Evaluation of Arm Loading on Walking Endurance and Breathing Response in Simulated COPD Patients: An Exploratory Physiological Cross-Sectional Trial"*)

EFL is a pathophysiological hallmark of COPD. Individuals with COPD typically experience breathlessness when performing exercise which can cause limitation of exercise capacity [17, 18]. A SR is a device that can be used to generate an EFL in a healthy individual thereby simulating an important clinical feature of COPD [30]. Several studies have investigated the effect of an externally applied SR generated EFL on exercise responses during incremental bicycle exercise. They reported a substantially decreased exercise performance and significant dyspnea on exertion [27-31]. A progressively increased $P_{ET}CO_2$ was also a consistent finding of in these studies [27-29]. All these earlier studies were however conducted with the SR applied only during cycle ergometry [27-32] and it therefore unknown if a SR can produce similar findings when applied during treadmill exercise.

This thesis evaluated the effect of an imposed EFL by application of a SR during incremental treadmill exercise on WLpeak, breathing pattern, metabolic parameters, and exercise limiting symptoms in healthy individuals. The overall aim was to evaluate the effect of EFL on exercise capacity, metabolic parameters, breathing pattern, dyspnea, and leg fatigue in healthy individuals by using a SR during symptom-limited incremental treadmill walking. Fifteen healthy non-smoking participants participated in the study. All participants completed two symptom-limited incremental tests, one with and the other without a SR, the order of which was randomized across participants.

The main findings of this study revealed that 1) WLpeak was significantly reduced in each participant when treadmill exercise was performed with the SR, indicating a reduction in the exercise capacity; 2) exertional dyspnea increased much faster with the SR during the

incremental treadmill exercise, and was reported to be the dominant exercise limiting symptom with the SR; 3) the exercise responses observed during incremental treadmill walking exercise in this study were consistent with previous findings obtained by studies which evaluated the effect of the SR during leg cycle ergometry; 4) the SR was able to simulate in healthy individuals the exercise limitation and increased symptoms observed in individuals with COPD performing incremental treadmill exercise.

To the best of our knowledge, this was the first study to show the impact of external EFL application using a SR during treadmill walking exercise on exercise performance and physiological responses in healthy individuals. Exercise performed in the presence of the SR provides an opportunity to evaluate the effect of pure EFL on pathophysiological responses in the absence of the peripheral muscle weakness. The SR model may also provide an opportunity for researchers to gain preliminary insight in studies conducted with healthy individuals while simulating severe COPD prior to going to a clinical population.

In conclusion, this study has contributed to the knowledge in evaluating the effect of external EFL by using a SR in healthy individuals during symptom-limited incremental exercise on a treadmill. External EFL led to a significantly reduced exercise capacity and severe dyspnea on exertion during exercise. The findings of this study were consistent with previous research obtained during EFL bicycle exercise. It suggested that a SR can simulate in healthy individuals the exercise limitations that are typically observed in COPD either on a treadmill or cycle ergometry.

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Appendix 1

$$grade(t) = \frac{\left[\left[\left(\frac{WR_{max}}{m \cdot g \cdot V_0}\right) - grade_0\right] \cdot t + 10 \cdot grade_0\right]}{\left[\left[\left(\frac{V_{max}}{V_0}\right) - 1\right] \cdot t + 10\right]} \quad (1)$$

- WRmax = projected maximum end-test work rate/the predicted peak work rate (based on the reference values of wattage)
- m = body mass in kilograms
- g = gravitational acceleration (9.81 m/s2)
- V0 = desired initial speed; 0.5mph (the lowest speed possible on the treadmill)
- Vmax = desired final treadmill speeds; 3mph (SR) or 4mph (NSR)
- t = time
- grade0 = initial grade; 1% (selected lowest grade on the treadmill other than 0%)

Adapted from Jone. (1997). [170]

Appendix 2

Table of modified Borg scale used for quantification of perception of dyspnea and fatigue	
Please rate the difficulty of breathing and leg effort during the exercise using the scale below, where 0 indicates no effort at all and 10 indicates the maximum tolerable level possible.	
0	Nothing at all
1	Very slight
2	Slight
3	Moderate
4	Somewhere severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximum)
10	Maximal