Acute Physiological, Symptomatic and Affective Responses to Exercise Training and Relationship with Exercise Adherence in Chronic Obstructive Pulmonary Disease

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ABSTRACT

Acute Physiological, Symptomatic and Affective Responses to Exercise Training and Relationship with Exercise Adherence in Chronic Obstructive Pulmonary Disease

Amanda Katy Rizk

Concordia University, 2014

Study Objectives: i) To describe and compare, in COPD patients, the acute physiological, symptomatic, and affective responses to continuous training at a high intensity (CTHI), continuous training at the ventilatory threshold (CTVT), and interval training (IT); ii) To examine the nature and degree of association between acute measures of intensity and adherence to a 12-week exercise-training program; iii) To investigate whether the relationship between acute responses and adherence is mediated or moderated by affect/vigor.

Methods: Thirty-five COPD patients (FEV_1 = 60.2 ± 15.8 % predicted) underwent baseline assessments, were randomly assigned to CTHI, CTVT, or IT, were monitored during a single exercise-training bout, and subsequently took part in a 12-week exercise-training program. Physiological, symptomatic, and affective responses were measured using a portable system, the PANAS and GVA questionnaires, and the Borg scale; respectively. Adherence was defined as the percent time spent within the target heart rate range for attended sessions.

Results: In comparison to CTHI, CTVT was associated with lower levels of RER, HR, and RR, whereas IT was associated with higher levels of $\dot{V}_E$, $\dot{V}_E$/MVV, RR, and a greater drop in SpO_2. Affective state generally improved from pre- to post-exercise, with increases in positive affect (F=9.74, p<0.001) and decreases in negative affect (F=6.43, p=0.005). The CTVT group experienced a greater dip in global affect mid-exercise compared to CTHI (p=0.04), yet had a higher level of end-exercise alertness compared to CTHI (p=0.01) and IT (p=0.02). The IT group reported the lowest levels of post-exercise alertness (p=0.04 versus CTHI and p=0.02 versus CTVT), and significantly lower 12-week adherence rates (F=6.69, p=0.004). Mean exercise $\dot{V}O_2$ (r=-0.466, p=0.007) and end-exercise global vigor (r=0.420, p=0.017) were most strongly correlated with adherence. The moderation model was supported, where end-exercise global vigor moderated the relationship between $\dot{V}O_2$ and adherence (β=2.74, t (32)=2.32, p=0.03).

Conclusion: Compared to CTHI, CTVT was associated with less physiological strain, and greater end-exercise alertness, while IT was associated with slightly more physiological strain, lower post-exercise alertness, and lower 12-week adherence rates. $\dot{V}O_2$ and end-exercise global vigor were most strongly associated with adherence. Acute end-exercise vigor was found to moderate the relationship between acute $\dot{V}O_2$ and adherence.

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"Live as if you were to die tomorrow. Learn as if you were to live forever"

-Mohandas Gandhi

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List of Acronyms

Alpha 1-antritrypsin (α 1- antritrypsin)

Body Mass Index (BMI)

Carbon Dioxide Excretion ($\dot{V}CO_2$)

Chronic Obstructive Pulmonary Disease (COPD)

Continuous Training at a High Intensity (CTHI)

Continuous Training at the Ventilatory Threshold (CTVT)

End-Expiratory Lung Volume (EELV)

Expiratory Reserve Volume (ERV)

Forced Expiratory Volume in 1 Second (FEV_1)

Forced Vital Capacity (FVC)

Functional Residual Capacity (FRC)

Global Vigor and Affect Instrument (GVA)

Heart Rate (HR)

Inspiratory Capacity (IC)

Inspiratory Reserve Volume (IRV)

Interval Training (IT)

Lung Diffusion Capacity for Carbon Monoxide (D_LCO)

Maximal Voluntary Ventilation (MVV)

Metabolic Equivalent of Task (MET)

Microsomal Epoxide Hydrolase 1 (mEPHx1)

Mild Cognitive Impairment (MCI)

Minute Ventilation ($\dot{V}_E$)

Negative Affect (NA)

One-Way Repeated Measures Analysis of Variance (ANOVA)

Oxygen Consumption ($\dot{V}O_2$)

Oxygen Saturation Pulse Oximetry (SpO_2)

Partial Pressure of Arterial Carbon Dioxide ($PaCO_2$)

Partial Pressure of Oxygen in Arterial Blood (PaO_2)

Peak Wattage (Wpeak)

Positive Affect (PA)

Positive and Negative Affect Schedule (PANAS)

Pulmonary Rehabilitation (PR)

Residual Volume (RV)

Respiratory Exchange Ratio (RER)

Respiratory Rate (RR)

Tidal Volume (V_T)

Total Lung Capacity (TLC)

Transforming Growth Factor Beta 1 (TGF-β1)

Tukey's Honestly Significance Test (HSD)

Tumor Necrosis Factor Alpha (TNFα)

Ventilation to Perfusion Ratio (V / Q)

Vital Capacity (VC)

Prologue

The choice to write a traditional over a manuscript-based dissertation came from my thesis committee and me. We felt that this format would better translate the endeavours underlying my dissertation work by presenting the three projects I undertook as a continuous story, as opposed to presenting the two resulting manuscripts, which do not mirror the events that occurred throughout my PhD in their chronological order.

Using the structure of a larger randomized clinical trial (OPTION) comparing the effects of three different exercise-training protocols on various pulmonary rehabilitation program outcomes, my PhD project aimed to study the acute physiological, affective, and symptomatic response to different exercise-training protocols in individuals with chronic obstructive pulmonary disease (COPD) and to subsequently examine the relationship between acute responses to training and exercise adherence in this patient population. The original goal was to publish three separate articles: a first one on the acute responses to the different exercise-training protocols in COPD, a second one on the methodology used to measure exercise adherence in our laboratory, and a third one on the relationship between acute responses to exercise training and subsequent exercise adherence in COPD.

The study on the acute responses to training was completed first, as planned, and the resulting manuscript was submitted to the peer-reviewed journal Chest in (February, 2013). The manuscript was rejected, and one of the main criticisms from reviewers was the parallel-group design of the study (as opposed to a crossover design). The acute study followed the design of the larger trial (OPTION), hence a parallel-group design with three intervention arms, and did not ask subjects to cross over to the other

interventions largely to spare them from additional measurements, given an already very demanding study participation. After the realization that this limitation would likely hurt the appreciation of the acute study as a stand-alone, the decision was made to wait for the 12-week exercise adherence data and to merge the papers originally planned as first and third into one larger, denser paper on the acute responses to exercise training and the relationship with exercise adherence in COPD. The rationale behind this decision is that the 12-week exercise adherence data will help justify the parallel-group design of the study and hopefully improve its perceived value. The updated manuscript will be submitted shortly to a strong peer-reviewed journal in respirology (Thorax).

The second paper on the methodology used to measure exercise adherence in our laboratory was completed as planned and recently published in the Journal of Visualized Experiments (JoVE). This paper presents a novel approach to measuring exercise adherence using continuous data tracking technology.

My dissertation therefore presents this body of work as a whole, while the resulting two manuscripts have been included in the Appendix section. Furthermore, a third manuscript that I have co-authored during my PhD, published in Chest, has been included in the Appendix and cited in my literature review. This paper presents results on the frequency and subtypes of mild cognitive impairment (MCI) in COPD patients who undertook our larger trial (OPTION), as well as a comparison of the mini-mental state examination (MMSE) and Montreal Cognitive Assessment (MoCA) as tools to detect MCI in COPD. My role included coordination of OPTION, which involved subject recruitment, scheduling of cognitive tests, data acquisition, and critically reviewing the manuscript.

To note, as my Master's and Ph.D. dissertation deal with the same clinical population, and due to my doctoral project being an extension of my Master's project, certain introductory sections of my Master's dissertation have been used in this document.

Overview

Chronic obstructive pulmonary disease (COPD) has a profound impact on the lives of individuals who suffer from it. Although COPD cannot currently be cured, it is possible to slow down disease progression with pulmonary rehabilitation (PR). Exercise training is considered the key to successful PR, as it is responsible for most of the benefits associated with this intervention. Current guidelines advocate high-intensity exercise training. However, this training intensity has been shown to be unachievable in a large proportion of patients. Alternative approaches, such as training at the ventilatory threshold and interval training, have been proposed as more physiologically and symptomatically tolerable and thus possibly easier to adhere to during an exercise training program.

The notion of an intensity-adherence trade-off has previously been described in the literature and believed to be mediated by affect (i.e., positive / negative pleasure responses). This relationship seems especially important during acute (or immediate) exercise. Indeed, in healthy individuals, the literature suggests that higher exercise intensities are negatively related to acute affect and adherence. In COPD, the acute responses to different exercise training protocols have been scarcely studied. To our knowledge, no study has investigated the acute affective response in this patient population. This leads us to the first objective, which is to compare, in COPD patients, the acute physiological, symptomatic, and affective responses to continuous high-intensity training, training at the ventilatory threshold, and interval training.

Several studies have investigated adherence to exercise training in COPD patients. However, large variability exists in the method used to measure adherence,

making it difficult to compare results across studies. Moreover, mostly indirect measures of adherence have been used thus far, resulting in adherence rates that do not necessarily reflect adherence to the prescribed training intensity. However, upon the arrival of continuous data tracking technology, the ability to monitor and record second-by-second data of several parameters during entire exercise-training bouts became available. However, this technology is limited in that it provides the raw values or a global mean of each parameter. This leads us to the second objective, which is to establish the methodology to use continuous data tracking technology to precisely measure adherence to an aerobic exercise-training protocol.

Finally, although certain predictors of pulmonary rehabilitation and, more specifically, exercise adherence have been identified in COPD patients, no published study has examined whether acute responses to various exercise-training protocols predict subsequent adherence to these protocols in COPD. Furthermore, the investigation of the role of affect as a mediator in the relationship between exercise intensity and adherence has yet to be made. This leads us to our third objective, which is to investigate the relationship between the acute responses to exercise-training and subsequent adherence to a 12-week training program by investigating whether affect/vigor mediated or moderated this relationship in COPD patients, and should these models not be supported, identify whether any acute responses independently predict adherence.

1. LITERATURE REVIEW

1.1 What is COPD?

COPD represents a cluster of respiratory disorders, which are mostly preventable and manageable, and associated with progressive and partially irreversible chronic airflow limitation [1-4]. The main symptoms of COPD, which typically appear in middle adulthood (≥ 55 years), are shortness of breath, cough, and sputum production [1, 4-7]. The two most common underlying disorders that lead to COPD are chronic bronchitis and emphysema [4]. Chronic bronchitis is clinically defined as the presence of cough and sputum production for at least 3 months in each of 2 consecutive years [1, 4]. Although chronic bronchitis is a main cause of COPD, it does not necessarily lead to chronic airflow limitation [1, 4]. Emphysema, on the other hand, is characterized by the destruction of the gas exchanging surfaces of the lungs (alveoli) [1, 4]. It is a pathological term that is often incorrectly used to designate COPD; however, emphysema refers specifically to the destruction of alveoli, which represents only one of the many abnormalities associated with COPD [1]. In actuality, COPD is a combination of airway disease (chronic bronchitis) and parenchymal destruction (emphysema), with the contributions of each varying from one patient to another [1].

1.2 Epidemiology

1.2.1 Prevalence, Incidence and Economic Burden

COPD is currently the fourth and fifth leading cause of death in Canadian women and men, respectively [8]. The province of Quebec has the second highest COPD-related mortality rate in the country after Nova Scotia [9]. Close to 800,000 Canadians, aged 35 and over, state that they have received a diagnosis of COPD from their physician, which accounts for approximately 4% of the population [3, 10]. The actual incidence and prevalence is probably higher since COPD is not diagnosed until clinically apparent and thus fairly advanced [1, 10, 11]. The proportion of individuals affected by COPD increases steadily with age in men and women [5]. Hence, the total morbidity and mortality rates associated with this disease are expected to rise over the next two decades as the population ages [1, 5, 7].

COPD imposes a heavy economic burden on the Canadian healthcare system. In 2004-2005, respiratory diseases ranked third as a major cause of hospitalization behind circulatory diseases and digestive disorders [10]. Among the respiratory diseases, COPD ranked first in that category, along with influenza/pneumonia [10]. In 2008, the average length of hospital stay for COPD exacerbations in Canada was 10 days with an average cost of approximately $10 000 per hospitalization [12]. Overall, respiratory diseases account for close to 7% ($8.63 billion) of total health care costs in Canada [10].

1.3 Risk Factors

1.3.1 Cigarette Smoking

Cigarette smoking, through the inhalation of respiratory irritants including noxious particles and gases, is by far the strongest preventable risk factor for this disease [1, 5, 13]. It is believed to be responsible for 80-90% of all COPD cases [5]. In fact, in the Obstructive Lung Disease in North Sweden (OLIN) study, it was reported that approximately 50% of smokers eventually developed COPD, as defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines [14]. The relative risk of developing COPD by means of cigarette smoking is dose-dependent and is often represented as total pack-years smoked (calculated by multiplying the number of packs smoked per day by the number of years smoked) [1, 15]. The discovery of smoking as a key risk factor has led to the incorporation of smoking cessation programs as a preventative treatment as well as an essential intervention for COPD patients [1].

1.3.2 Genetic

To date, the best documented genetic risk factor for COPD is a genetic deficiency of alpha 1-antitrypsin (α1-antitrypsin), which predisposes individuals to COPD [1]. This genetic deficiency affects approximately 1 in 2000-5000 individuals [16]. The main function of alpha-1-antitrypsin is to protect the lung from proteolytic damage from neutrophil elastase [16]. With a deficiency of alpha 1-antitrypsin, a greater secretion of neutrophil elastase occurs during inflammation [17]. Neutrophil elastase is an enzyme that promotes or leads to proteolysis (a breakdown of protein) thereby destroying bacteria and host tissue [17].

This risk of developing emphysema is amplified in individuals whose mothers smoked during pregnancy and who then themselves smoked later in life, which highlights the importance of the interaction between the genetic and environmental risk factors [1, 18].

Other genes, which regulate the production of transforming growth factor beta 1 (TGF-β1) [19], microsomal epoxide hydrolase 1 (mEPHX1) [20], and tumor necrosis factor alpha (TNFα) [21], have also been associated with the pathogenesis of COPD. However, further studies are needed to clarify the association of these genetic factors with this disease.

1.3.3 Occupational Exposure to Dusts and Fumes

Occupational exposure to organic and inorganic dusts and chemicals (vapors, irritants, and fumes) are also known to cause COPD, independent of smoking history [22]. Although the risk is less than that caused by cigarette smoking alone, it continues to remain an underestimated risk factor [1]. According to the American Thoracic Society [23], occupational exposure accounts for up to 20% of all COPD cases. Results from a large population-based study consisting of data from 9,823 subjects aged 30-75 years [22], confirmed these findings by revealing that the fraction of COPD attributable to occupational exposure was approximately 19.2% overall, and 31.1% among individuals who never smoked. Authors further reported on the most common occupations associated with COPD, which included freight, stock, and material handlers; records processing and distribution clerks; sales; transportation-related occupations; machine operators; construction trades; and waitressing jobs [22].

1.3.4 Air Pollution

Exposure to indoor and outdoor air pollution has been shown to increase the risk of developing COPD, aggravate respiratory symptoms of those who have already received a diagnosis, and increase mortality [1, 10]. Indoor air pollution can arise through the presence of second-hand smoke, smoke created by the burning of wood, mould, radon gas, formaldehyde gas, animal dung, crop residues, and coal burned in open fires and poorly operating stoves [1, 10]. The risk of indoor air pollution caused by biomass cooking and heating continues to grow especially among women in developing countries who continue to use biomass and coal as their main source of energy for cooking and heating [1]. Outdoor air pollution, on the other hand, can be composed of a variety of gases and particulate matter [10]. Air contaminants of interest to respiratory health include nitrogen dioxide, sulphur dioxide, carbon monoxide, ground level ozone, and particulate matter with a diameter of less than 2.5 microns [10]. Such contaminants can be caused by fossil fuel combustion mainly from vehicle emissions, burning of wood, industrial emissions, and manufacturing processes [10].

1.3.5 Infection

Viral and bacterial infections also contribute as a risk factors in COPD and play a major role in exacerbations [1]. A history of severe childhood respiratory tract infections is associated with increased respiratory symptoms and decreased lung function [1]. Childhood infections are also related to having a low birth weight, which is also associated with COPD [1, 24]. Furthermore, HIV infection and a history of tuberculosis have also been associated with airflow obstruction in COPD patients [1, 25, 26].

1.4 Pathology, Pathogenesis and Pathophysiology of COPD

1.4.1 Pathology and Pathogenesis

The cascade of events leading to COPD, as illustrated in **Figure 1,** begins with exposure to specific risk factors linked to this disease, such as inhalation of smoke and particulates [1, 2], which injures lung tissue and leads to inflammation [1, 2]. More specifically, white blood cells, including lymphocytes (T $CD4^+$, T $CD8^+$), macrophages, and neutrophils, are recruited to sites of injury. These cells subsequently release inflammatory mediators such as lipid mediators (leukotriene B_4), chemokines (interleukin-8), cytokines (interleukin-1 beta, interleukin-6, TNFα), and growth factors (TGF-β1), which interact with structural cells in the airways and alveoli [27]. This interaction induces chronic inflammation in various regions of the lung and structural changes resulting from recurring tissue damage and repair [27]. In addition, chronic inflammation can be brought on by oxidative stress and an imbalance between proteases (which break down connective tissue) and antiproteases (which protect against this breakdown), at the favour of the former [2, 27]. This imbalance may cause the breakdown of elastin to occur, a classic sign of emphysema, thereby diminishing the elastic ability of the lungs [1, 2].

In general, pathological structural changes occur in four distinct regions of the lung: the proximal (central) airways, the peripheral airways, the lung parenchyma, and the pulmonary vasculature [1, 2]. The proximal airways refer to the trachea and bronchi with an internal diameter > 2 mm [27]. Structural changes occurring in this region include an increase in goblet cells, hypersecretion of mucus caused by enlarged submucosal glands, and squamous metaplasia of the epithelium (the reversible replacement of

columnar epithelium with squamous epithelium, thereby altering the normal homeostatic state) [27]. The peripheral airways include the bronchioles with an internal diameter < 2 mm [27]. Potential structural changes occurring in this region include inflammation, thickening of the airway wall, narrowing of the airway, peribronchial fibrosis, and exudate (fluid accumulation in areas of inflammation) [27]. Lung parenchyma consists of the respiratory bronchioles, alveolar ducts, and alveoli [27]. Structural changes in this region include destruction of the alveolar wall and apoptosis (programmed cell death) of epithelial and endothelial cells [27]. The pulmonary vasculature refers to all the vessels (arteries, veins, and capillaries) found in the lungs, and an increase in smooth muscle mass, endothelial cell dysfunction accompanied with thickening of the intima, which can all lead to pulmonary hypertension has been observed in this patient population [27]. It is important to note that the extent to which each region is affected varies from one COPD patient to another based on disease severity, whether the individual continues to smoke, and the degree of contribution of chronic bronchitis and emphysema [1, 2].

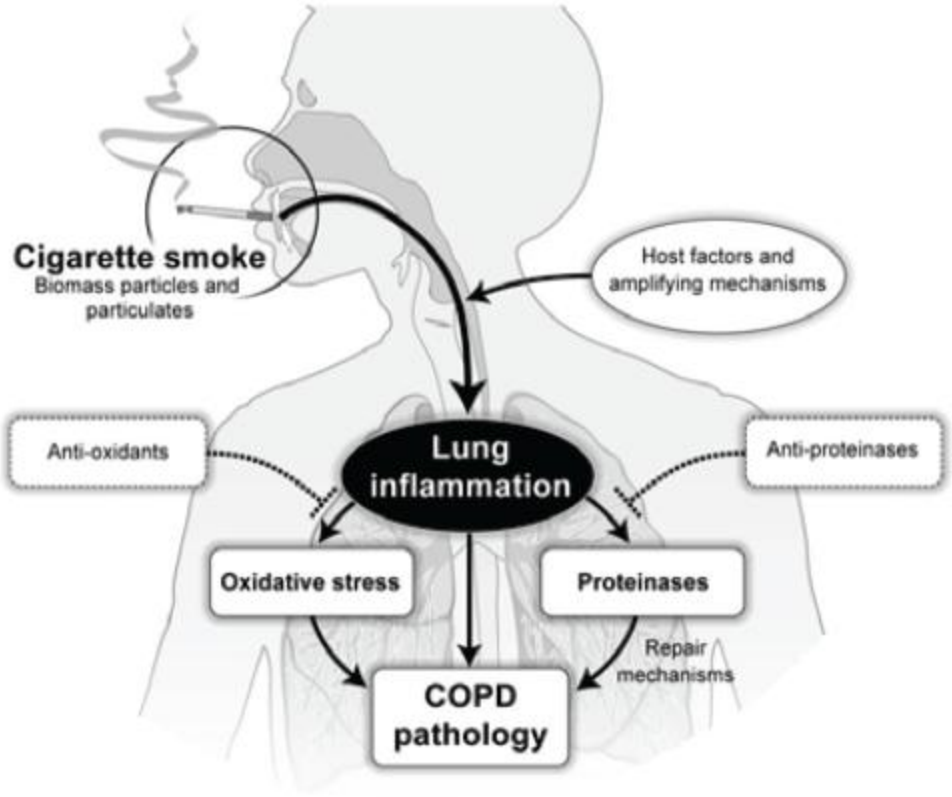


Figure 1. Pathogenesis of COPD.

Taken from GOLD 2010 Update [27]

1.4.2 Pathophysiology

1.4.2.1 Expiratory Flow Limitation and Lung Hyperinflation

In order to comprehend the complexity of expiratory flow limitation and lung hyperinflation, which are classic features of COPD, it is important to first gain background knowledge of basic lung volumes, capacities, and flow rates. **Figure 2** illustrates these basic lung volumes, capacities, and flow rates. There are four basic lung volumes as well as four basic lung capacities. When one is breathing normally, at rest, the regular inspiratory / expiratory cycle of breathing is termed tidal breathing [28]. The

volume of air breathed in and out through each breath during tidal breathing is called tidal volume (V_T). Inspiratory reserve volume (IRV) is the maximum amount of additional air that can be inspired from the end of a normal inspiration, while expiratory reserve volume (ERV) is the maximum amount of additional air that can be expired from the end of a normal expiration. Finally, residual volume (RV) is the amount of air remaining in the lungs after a maximal forced expiration [28]. In normal lungs, the RV represents the relaxation of all respiratory muscles in addition to the balance of recoil pressures between the lungs and chest wall [28].

Lung capacities are composed of two or more lung volumes. Inspiratory capacity (IC) is the amount of air that can be inhaled forcefully subsequent to a normal expiration and corresponds to the sum of IRV and V_T [28]. At the end of a normal expiration, the volume of air contained in the lungs is termed the functional residual capacity (FRC), also known as the end-expiratory lung volume (EELV), and corresponds to the sum of ERV and RV [28, 29]. Vital capacity (VC) is the amount of air that can be forcefully exhaled following a maximal inspiration and corresponds to the sum of IRV, V_T, and ERV [30]. Finally, total lung capacity (TLC) is the total volume of air that can be contained in the lungs at the end of a maximal inspiration and corresponds to the sum of all four basic lung volumes (IRV, V_T, ERV, and RV) [28].

Several flow rates can be measured, yet the two of greatest interest and clinical usefulness in COPD are forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC). Both of these measurements can be obtained through spirometry with a FVC manoeuvre, which requires patients to take a deep breath in and forcefully expire as much air as possible as quickly as possible following certain standards [31]. FEV_1

represents the amount of air that is exhaled in the first second of the FVC manoeuvre [30]. Its value in litres and in percentage of the normal predicted value is pivotal in the classification of COPD disease severity. Likewise, the ratio of FEV_1 to FVC, which provides an indication of the proportion of FVC exhaled in the first second of expiration, is critical in the diagnosis of COPD [28].

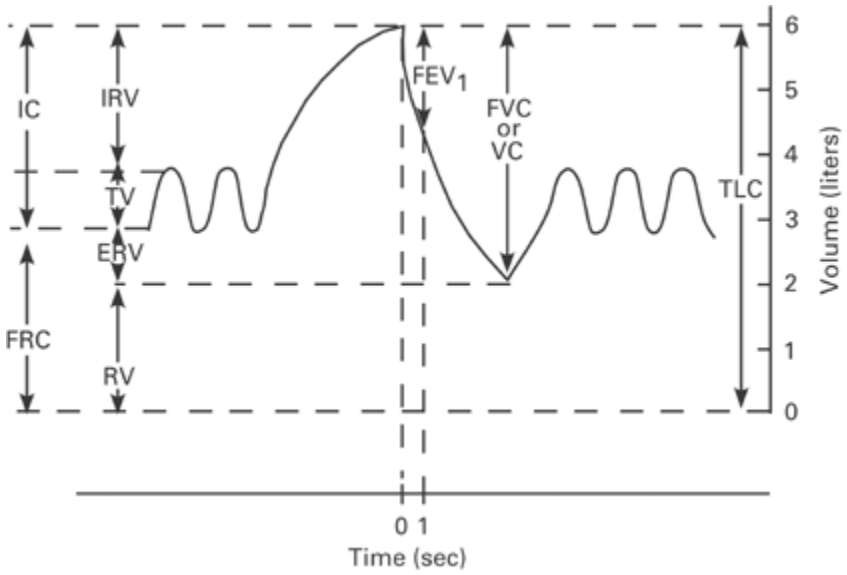


Figure 2. Basic lung volumes, capacities, and flow rates. IC: inspiratory capacity; FRC: functional residual capacity; IRV: inspiratory reserve volume; TV (also written as V_T): tidal volume; ERV: expiratory reserve volume; RV: residual volume; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; VC: vital capacity; TLC: total lung capacity.

Taken from Chien et al. [32]

The hallmark feature of COPD is expiratory flow limitation, as shown by a reduction in the FEV_1 / FVC ratio, often accompanied by a reduction in FEV_1 [28, 33]. This outcome arises due to intrinsic and extrinsic factors [33]. Such factors include mucosal inflammation and oedema, mucus hypersecretions, extraluminal compression by adjacent overinflated alveoli, ciliary dysfunction, gas exchange abnormalities, etc. [33]. Emphysema, characterized by a loss of lung elasticity, further limits respiration by

reducing the elastic recoil pressure in the lungs, which increases the resistance to expiratory airflows, thereby increasing the expiratory pressure needed to exhale, making it progressively more difficult to expire [33]. Patients with COPD also often have an increased physiological dead space, which in this case refers to air that does not take part in gas exchange due to , and caused by the destruction of alveoli and loss of gas exchange surfaces [34]. Due to this physiological limitation causing inefficient gas exchange between alveoli and surrounding vasculature, patients with COPD have an increased ventilatory requirement for any given task [35].

Patients with COPD also often experience some degree of lung hyperinflation, also commonly known as air trapping, which is intimately linked to the sensation of dyspnoea [28]. Hyperinflation can be thought of as having two main components; static hyperinflation and dynamic hyperinflation. Static hyperinflation is caused by a loss of elasticity in the lung parenchyma, thereby causing a reduced amount of recoil pressure from the lungs to counter the pressure exerted by the chest wall [28]. Static hyperinflation can be considered if values of resting FRC or EELV are elevated above normal values (Figure 2) [28]. Dynamic hyperinflation refers to an elevation of EELV, which could be brought on by exercise or anything that will increase minute ventilation ($\dot{V}_E$) (e.g., emotional stress) [36]. It is caused by additional air trapping within the lungs following each breath due to the individual being unable to completely empty their lungs upon exhalation, therefore causing disequilibrium between inspired and expired volumes [28]. Several factors could be associated with the degree of hyperinflation in COPD patients such as inflammation, increased mucus production, narrowed airways, and possible collapsing of the airways [28, 37]. Both the static and dynamic effects contribute to lung hyperinflation in this disease, yet dynamic hyperinflation typically occurs more

frequently. Additionally, dynamic hyperinflation can occur independent of static hyperinflation [28]. Hyperinflation can cause several unfavourable effects, including an increase in the amount of work needed to breathe, an impairment in gas exchange between alveoli and blood vessels, and possible respiratory muscle dysfunction [28].

1.4.2.2 Gas Exchange Limitations

In an emphysematous lung, parenchymal destruction limits oxygen from entering the pulmonary capillaries to subsequently reach the systemic circulation, and carbon dioxide from entering the alveoli to be expired [38, 39]. Furthermore, structural abnormalities of the pulmonary arteries have been observed [40]. In emphysema, both aberrations are present, where both ventilation of the lungs and perfusion of the pulmonary capillaries will decrease to a similar extent, thus retaining normal ventilation to perfusion ratio (V / Q). In chronic bronchitis, should specific areas of the lung be under ventilated, a mismatch between ventilation and perfusion exists, as reflected by a drop in the V / Q ratio [38, 39]. Patients, therefore, require more ventilation to maintain adequate gas exchange compared to their healthy counterparts [38]. In most cases, the transfer of gases worsens as disease severity progresses and gas exchange becomes inadequate to meet the needs, resulting in hypoxemia (a decreased partial pressure of O_2 in the blood) and hypercapnia (increased levels of CO_2 in the blood) [41]. The arterial perfusion of oxygen (the amount of oxygen being diffused from pulmonary arteries to alveoli), the V / Q, and the partial pressure of O_2 in arterial blood (P_aO_2) are all indicators of emphysema severity [41].

1.4.2.3 Respiratory Muscle Dysfunction

Muscle dysfunction is a classic systemic feature of COPD and has been associated with reduced quality of life and increased mortality [42-44]. The main muscle groups that support inspiration are the diaphragm, external intercostals, and scalenes [38, 45]. These muscles expand the thoracic cage volume, thereby creating a negative alveolar pressure allowing for an inward air flow to occur [45]. Accessory muscles, including the parasternal and sternocleidomastoid, are normally only recruited while coughing or exercising in healthy individuals [38]. However, in COPD patients, it is not uncommon for these muscles to be activated during quiet breathing (at rest), due to the increased work of breathing at rest [38]. Expiration is mainly a passive action a rest, however in COPD patients, the internal intercostals are often recruited due to static hyperinflation [38, 45].

In COPD, the major inspiratory muscles are set at a functional disadvantage due to an increased mechanical load [38, 45]. This increased mechanical load is brought about through increased elastic loads (caused by adaptations to the thorax wall, and a decreased static lung elastance due to parenchymal destruction), resistive loads (caused by narrowing of the airways due to inflammation, mucosal oedema, mucus accumulation, and airway fibrosis) and threshold loads (such as the intrinsic positive end-expiratory pressure; a pressure threshold caused by incomplete exhalation that must be overcome for the next inspiration to take place) [33, 38, 45]. During the early stages of the disease, the inspiratory muscles of patients with COPD generate a greater force as compared to healthy individuals as a result of their exposure to greater work demands [46]. However, COPD patients also experience hyperinflation, which places the respiratory muscles at a disadvantage (i.e. muscle fiber shortening and a suboptimal

length / tension relationship) [47]. Due to this muscular disadvantage, the diaphragm begins to remodel itself to adapt to the physiological needs [46]. In an effort to adapt, sarcomere number has been reported to decrease, resulting in a shortened resting muscle length, thus placing the muscle in a suboptimal length to generate force (i.e. pressure) [38, 48]. This alters the geometry of the thorax wall, thereby decreasing inspiratory pressure and maximal transdiaphragmatic pressure [38, 45]. Furthermore, protein degradation, muscle wasting, decrease in myosin content, and neuromechanical uncoupling reduces the ability and capacity of the inspiratory muscles to generate adequate pressures to maintain minute ventilation [38]. An additional insult brought on by chronic low level inflammation and oxidative stress, which impairs specific muscle fiber pressure generation and increases sarcomere disruption in the diaphragm, also significantly reduces respiratory muscle force generation in COPD patients [38].

In return, respiratory muscle endurance is enhanced in COPD as a result of a morphological/phenotypic shift in muscle-fiber type from type IIa glycolytic fibers towards more fatigue resistant, slow-twitch, oxidative type I fibers [38, 48-50]. This adaptive response has been observed in the diaphragm and parasternal muscles and has been shown to be positively correlated with disease severity [38]. Another adaptive mechanism associated with more fatigue resistance in respiratory muscles is an increase in mitochondria linked with adaptations related to energy production [38, 48]. These mechanisms include an increased oxidative capacity, increased mitochondrial respiratory chain enzyme activity, increased capacity to generate ATP, reduced energy cost for isometric contractions, as well as greater dependence of glucose for energy production [38].

Acute exacerbation in COPD, defined as an aggravation of respiratory symptoms beyond normal day-to-day variation, is also characterized by increased lung resistance, increased work of breathing, increased ventilatory demands, rapid and shallow breathing pattern, dyspnoea, and an increased EELV, all contributing to hyperinflation [38, 51]. An increased recruitment of the rib cage muscles and expiratory muscles is also observed [38]. Central drive is proportionately increased to meet the extra physiological demands [38]. However, the respiratory pump is less effective due to the decrease in the capacity to generate force [38]. The increased load placed on the inspiratory muscles can be quantified using the pressure-time product of the inspiratory muscles [38]. A greater pressure-time product is indicative of a greater oxygen consumption, muscle fatigue, and load placed on inspiratory muscles [38]. During acute exacerbation, the load has been shown to increase and to be close to the critical value of 0.15 [38].

Despite all the attempts to counteract the physiological and biochemical abnormalities associated with COPD, these adaptations unfortunately do not surpass or even meet the additional challenges brought on by exercise and/or acute exacerbations [38]. Collectively, the overall and sustained respiratory dysfunction can lead to respiratory muscle fatigue and respiratory pump failure [38].

1.4.2.4 Peripheral Muscle Dysfunction

Peripheral muscle dysfunction has been identified as another important systemic consequence associated with this disease. The quadriceps, more specifically the vastus lateralis muscle, has been the most studied muscle group linked to peripheral muscle fatigue [45, 52]. Interestingly, the opposite shift observed in respiratory muscles has

been reported in peripheral muscles of COPD patients; indeed, a shift from type I to type IIb fibers occurs in these muscles [45, 52, 53]. This fiber type switch to a more fatiguable fiber type results in premature muscle acidosis, accumulation of lactate, and leg fatigue a relative low workloads compared to matched healthy controls [53]. Additionally, a decrease fiber cross-sectional area has been observed, which is linked to muscle atrophy, as well as a decrease in capillary contact with fibers [54]. Due to these structural changes, a plateau in leg blood flow and leg oxygen consumption often occurs during exercise [55]. Patients who exhibit a plateau in leg blood flow have higher levels of ventilation and dyspnoea compared to those that do not plateau, suggesting that blood flow is unable to match increasing workloads and blood flow from peripheral muscles may therefore be redirected to the respiratory muscles, a process known as the steal effect [55, 56]. Finally, the clinical importance of peripheral muscle dysfunction as an outcome has also been demonstrated in the literature, where muscle wasting has been shown to impact survival in patients with an FEV_1 < 50% predicted [57, 58]. Moreover, mid-thigh cross-sectional area has been shown to be a better predictor of mortality than BMI (body mass index) [58].

1.4.2.5 Exercise Intolerance

Exercise intolerance is a complex consequence of COPD [59]. It is closely related to disability/impairment, and is a strong predictor of quality of life [39, 59]. Exercise intolerance can stem from a multitude of intricate mechanisms and interactions frequently present among patients with COPD. These include a reduced ventilatory capacity (reduced expiratory flow rates), a decreased exercise capacity (decrease in peak work rate, maximal oxygen uptake ($\dot{V}O_2$) or endurance time to constant-load

exercise), the presence of dynamic hyperinflation (decrease in IC), symptom perception during exercise (dyspnoea and leg fatigue being reached at lower intensities), hypoxemia (oxygen desaturation), and peripheral muscle fatigue [59]. The contribution from each of these factors varies greatly from one individual to another and will depend on disease severity, disease characteristics (i.e. proportion of emphysematous and chronic bronchitis components), and degree of exercise intolerance due to deconditioning [39, 59].

Patients with mild COPD will often have similar exercise responses compared to healthy individuals; including a normal $\dot{V}O_2$ / work rate relationship and $\dot{V}O_2$ max [39]. In moderate to severe COPD, the increased work of breathing at rest is further exacerbated during exercise [38, 39]. This can be explained by a reduction in the capacity for gases to diffuse due to greater dead space ventilation and inefficient gas exchange as observed by a mismatch in the V / Q ratio [39, 59, 60]. Other causes can include an hypoxemia, and an increased stimulation of lung receptors, which are meant to increase $\dot{V}_E$ and to decrease partial pressure of arterial carbon dioxide (P_aCO_2) [39]. The breathing pattern adopted by COPD patients during exercise is characterized by more rapid (increase in respiratory rate) and shallow (decrease in V_T) breathing compared to healthy individuals at the same $\dot{V}_E$; this phenomenon has been found to be associated with rib cage muscle fatigue [38, 39, 61]. During exercise, COPD patients will increase their minute ventilation as do healthy individuals, but will do it mostly via an increase in respiratory rate (RR), to compensate for the increased ventilatory demand [37]. This increase in respiratory frequency will reduce the time between breaths, thus making it increasingly difficult to fully empty the lungs [37]. Additionally, EELV rises,

expiratory muscle pressure increases, while inspiratory capacity decreases [39, 48, 62]. This vicious cycle will result in dynamic hyperinflation and could thus lead to premature exercise termination due to breathlessness [37]. Dynamic hyperinflation further increases the elastic inspiratory work of breathing by increasing the load and decreasing the capacitance [38]. Consequently, the mismatch in the V / Q relationship is further aggravated [38].

Towards the end of exercise, in contrast to their healthy counter-parts, COPD patients have a decrease in their ventilatory reserve observed by levels of $\dot{V}_E$ that reach their predicted maximum voluntary ventilation (MVV), estimated from resting FEV_1 (FEV_1 x 35) [59, 63, 64]. In other words, the ratio of $\dot{V}_E$ / MVV can reach or exceed 100%, whereas it rarely surpasses 80% in healthy individuals, and the end-inspiratory lung volume approaches TLC [39, 59]. When end-inspiratory lung volume approaches 90% of TLC, the elastic load to breathing is increased [39]. At this point, the accessory muscles take on the additional load and when no longer bearable, inspiratory muscle fatigue ensues leading to hypercapnia and pump failure [38, 39].

Leg fatigue is another symptom often reported by patients with COPD as a limiting factor to exercise, prior to the occurrence of physiological limits (e.g., $\dot{V}O_2$) [59]. A study conducted by Saey and colleagues [53] examined the relationship between muscle fatigue and exercise response and showed that even after the administration of a bronchodilator, patients with greater susceptibility to leg fatigue did not obtain a significant improvement in exercise capacity with bronchodilation. This demonstrates that peripheral muscle dysfunction may play a significant role in exercise intolerance

among COPD patients [53]. It is important to note that the type of exercise modality chosen (e.g. walking versus cycling) seems to affect the degree and the source of exercise intolerance in this patient population [59, 65]. A study conducted by Pepin and colleagues [65] compared the response of COPD patients during a cycle endurance test to their response during an endurance shuttle walk test. The cycling test was found to induce greater levels of perceived leg fatigue as compared to the walking test, whereas the shuttle walk test induced greater levels of dyspnoea [65].

As the causes and mechanisms contributing to exercise intolerance are multi-factorial and involve various systems, it is important to consider all aspects when assessing exercise intolerance.

1.4.2.6 Pulmonary Complications

Respiratory exacerbations are the most frequent pulmonary complication among COPD patients. According to the American Thoracic Society and European Respiratory Society [2, 41], an exacerbation of COPD is defined as “an event in the natural course of the disease characterised by a change in the patient’s baseline dyspnoea, cough and/or sputum beyond day-to-day variability sufficient to warrant a change in management”. On average, COPD patients experience two exacerbations per year and approximately half of all exacerbations are caused by acquiring an infection [3]. Management of an exacerbation should include careful assessment along with an increased dosage of inhaled short-acting beta$_2$-agonist and/or an anticholinergic drug [3]. Antibiotics and/or oral corticosteroids are also often prescribed during this time [3]. If severe enough, patients might also be prescribed oxygen therapy [3]. To date, there is no classification

of exacerbations that has been established [2, 41]. However, several well-known indicators exist such as the requirement of hospital admittance, the presence of a high-risk co-morbid condition, an obvious increase in dyspnoea, difficulty sleeping or eating, worsening hypoxemia and/or hypercapnia, changes in mental status, uncertain diagnosis, inadequate home care, and the inability for the patient to care of themself [2, 41].

Aside from exacerbations, COPD patients can be faced with other pulmonary complications such as pulmonary hypertension [66]. Pulmonary hypertension evolves as a result of the constriction of pulmonary arteries, making it much more difficult for the right heart to pump blood through the pulmonary circulation [67]. Eventually, this resistance in the lung circulation may result in vascular remodelling, such as thickening of the blood vessels (intimal hyperplasia) and smooth muscle hypertrophy [67]. In addition, as blood pressure rises within the lungs, the heart's right ventricle has to pump to a greater extent thereby causing hypertrophy of the myocardium [67]. Due to the greater workload exerted on the heart, right heart failure could ensue [41]. Right heart failure, also known as cor pulmonale, occurs when the right heart in unable to supply sufficient blood supply to the lungs in order for re-oxygenation to occur; this then affects oxygenated blood supply to the left heart and subsequently to the rest of the body [67].

1.4.2.7 Anxiety and Depression

Like in many other chronic diseases, patients with COPD tend to present with both anxiety and depression [41]. However, they are the least-treated comorbidities of COPD [68]. In a systematic review of 64 studies, comparing rates of anxiety and

depression in various diseases, the prevalence of depression in COPD patients was found to range from 37 to 71%, and that of anxiety from 50 to 75%; this was comparable to other chronic diseases including renal disease, heart disease, AIDS, and cancer [69]. Surprisingly, less than one third of COPD patients received appropriate treatment [70, 71]. If left untreated, depression and anxiety can have major implications, such as increased number of physician consultations, increased frequency of hospital admission, prolonged hospital stay, lower treatment adherence, as well as poor quality of life and premature death [71]. In a recent review, conducted by Laurin et al., authors provided evidence that COPD patients with anxiety and/or depression had an increased risk of exacerbation [72]. Depression among COPD patients has also been found to predict dyspnoea, fatigue, and disability [73, 74]. Symptoms of depression include hopelessness, pessimism, difficulties concentrating, and social withdrawal [75]. Symptoms of anxiety include difficulties concentrating, sweating, tachycardia, and dyspnoea [68]. Possible treatments consist of pharmacotherapy and psychotherapy [68].

1.4.2.8 Cognitive Dysfunction

One of the extrapulmonary manifestations observed in COPD is cognitive dysfunction and has been associated with increased disability, impaired functioning in daily life, poor adherence to treatment, and mortality [76-79]. Cognition is a term used to describe higher order neural processes that support information handling [80]. However, a theoretical definition of cognitive dysfunction has yet to be established in this patient population [81]. Cognitive function is normally composed of several domains which include but are not limited to reception/perception, learning ability, memory, processing, physical expression, and attention/consciousness [80]. In a multicenter clinical trial

including 203 COPD subjects, cognitive impairment was found in 42% of subjects as compared to 14% in healthy controls [82]. In the same cohort, cognitive impairments were found in 27% of COPD patients with mild hypoxia and the rate increased to 61% in individuals with severe hypoxia [83]. Similarly, Incalzi et al. reported that 48.5% of COPD patients have cognitive decline [84]. Furthermore, in a recent study conducted by our team in collaboration with a team specialized in neuropsychology, it was estimated that approximately 36% of moderate to severe COPD patients have a mild cognitive impairment (MCI), compared to 12% in healthy age-matched controls (refer to appendix for full published manuscript) [85]. The importance of identifying MCI has been confirmed in longitudinal studies where approximately half of individuals with mild cognitive impairment develop dementia in five years time [81], and among individuals who develop dementia, 60% will develop Alzheimer's disease [86]. In a systematic review of 15 studies [87], the domains found to be most affected in COPD were memory and attention. Coordination and learning abilities were also found to be impaired [87]. Proposed mechanisms contributing to cognitive dysfunction include neuronal damage caused by hypoxia, inflammation, cerebral hypo-perfusion, and abnormalities to cerebral microcirculation [87, 88]. PR has been associated with improved cognitive function during acute and chronic exercise [89, 90]. It has been suggested that an increase in blood flow to the brain and an increase in neurotransmitter release improves cognitive function [89-91]. In a study conducted by Etnier et al. [91], age, fitness level, and pulmonary function were all predictive of cognitive performance in this patient population.

1.5 Clinical Assessment of COPD

1.5.1 Diagnosis

Individuals with a history of significant exposure to the potential risk factors and with comorbidities should be screened for possible diagnosis [2]. To diagnosis COPD, a spirometry test is required [1, 2]. Spirometry is a common pulmonary function test that measures expiratory flow rates and three of the four lung volumes (all except RV) [1, 31]. It is recommended that a spirometry test be performed after a bronchodilator is administered (e.g. 400 µg salbutamol) [2]. Patients must have a post-bronchodilator FEV_1 / FVC ratio ≤ 0.7 to confirm the presence of airflow limitation that is not fully reversible [1, 2]. Using the results, disease severity can be classified using GOLD stages 1 through 4 ranging from mild to very severe disease (see Table 1) [1].

Table 1. Spirometry classification of COPD severity based on post-bronchodilator FEV_1.

Stage	Severity	FEV_1 % predicted	Post-Bronchodilator FEV_1 / FVC
I	Mild	≥ 80	< 0.70
II	Moderate	50 - 80	< 0.70
III	Severe	30 - 50	< 0.70
IV	Very severe	< 30	< 0.70

FEV_1: forced expiratory volume in one second; FVC: forced vital capacity.

Adapted from GOLD [1]

1.5.2 Investigations

Further investigations should include a thorough medical history, a physical examination, and an exercise test if indicated [1]. A detailed history should be conducted for any patient suspected of having COPD and should include the following: past medical history, family history of COPD, identification of risk factors and possibilities for

reducing them, pattern of symptom development, history of previous exacerbations and hospitalizations, presence of comorbidities, appropriateness of current medical treatments, impact of disease on patient's life, and family/social support [1, 2]. Patients with airflow limitation in their 40's or 50's and especially those with a family history of COPD should also be tested for α-1-antitrypsin deficiency [1, 2].

A physical assessment is important to detect any signs of COPD prior to disease progression. Physical signs are infrequently diagnostic in nature due to the fact that they are typically not apparent until significant impairment of lung function has already transpired [1]. During assessment, medical examiners should look for the following signs: central cyanosis (bluish color), chest wall abnormalities (horizontal ribs, barrel chest, protruding abdomen), flattening of the hemi-diaphragms, accelerated heart rate, shallow breathing, pursed-lip breathing, resting respiratory muscle activation while supine, and ankle/lower leg oedema [41]. In addition to an examination, a medical evaluator should palpitate surrounding areas in addition to listening for any wheezing or inspiratory crackles [41].

Cardiopulmonary exercise tests are often conducted in patients with COPD and performed on either a cycle ergometer or a treadmill [1]. Indications for clinical exercise testing in this population include evaluating exercise capacity for prognosis, impairment/disability assessment and/or exercise prescription, identifying factors that contribute to exercise limitation, and/or evaluating the impact of therapeutic interventions on exercise capacity and exercise response [39]. Walking tests, such as the 6-minute walking test [39] and the shuttle walking tests [92], are also used in this patient population to assess disability and/or the functional impact of treatment.

1.6 Management of COPD

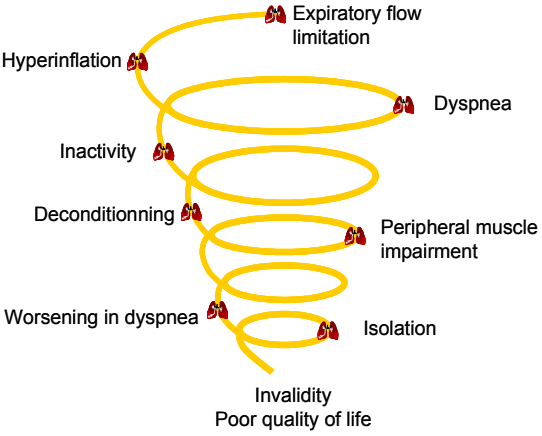


Figure 3. COPD downward spiral. Adapted from la Clinique du Souffle la Solane, Osséja, France.

COPD is a preventable and manageable disease [3, 41]. Although this disease cannot be cured with current available therapy, it is possible to slow down a patient's descent through the downward spiral (**Figure 3**) with modern management of the disease [7, 93]. Treatment should include a management strategy combining pharmacotherapy and non-pharmacotherapeutic interventions [3]. The goals of such interventions are to prevent disease progression, reduce the frequency and severity of exacerbations, improve health-status, improve health-related quality of life, and reduce mortality [3]. A comprehensive approach, as illustrated in **Figure 4**, has been suggested for optimal management of COPD [3].

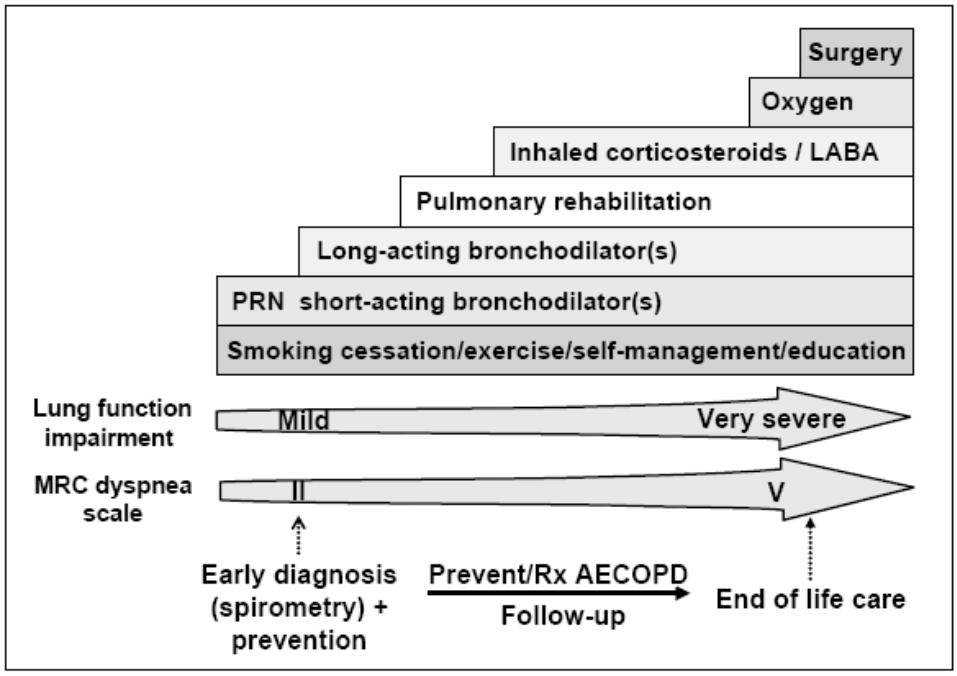


Figure 4. A comprehensive approach to the management of COPD. AECOPD = Acute exacerbation of COPD; LABA = long-acting beta$_2$-agonist; MRC = medical research council; PRN = as needed; Rx = treatment.

Taken from CTS COPD recommendations [33]

1.6.1 Smoking Cessation

Tobacco is a highly addictive substance and tobacco smoking is considered a chronic relapsing disorder [2]. Smoking cessation programs are the single most effective and cost-effective strategy for preventing and treating those with COPD and should therefore be considered as the primary intervention [3, 41]. Approximately 41% of smokers try to quit smoking every year; however only 10% achieve and maintain this goal [3]. Thus, it is imperative that all smoking COPD patients or those at risk of developing this disease be offered a smoking cessation intervention in order to increase the chances of cessation [3, 41]. Effective interventions include counselling from physicians and other health care professionals, self-help and community based

programs, as well as medications [41]. The use of medications such as nicotine replacement therapy (gums, transdermal patches, and nasal sprays) and antidepressant bupropion, approximately doubles smoking cessation rates [3]. Recent evidence has also suggested that exercise training can be used as an aid to smoking cessation [94, 95].

1.6.2 Self-Management Education

Self-management plays an important role in COPD. According to Bourbeau et al. [96], self-management is a term used to describe “any patient education program aimed at teaching skills needed to carry out medical regimens specific to the disease, guide health behaviour change, and provide emotional support for patients to control their disease and live functional lives”. The same authors conducted a multi-centered randomized controlled trial examining the impact of a self-management program on the use of hospital services and health outcomes among moderate to severe COPD patients [96]. The self-management program through disease specific education (“Living Well with COPD”), weekly and monthly follow-up phone calls, and the availability of case managers for advice and treatment supervision was shown to reduce hospital admissions, emergency department and unscheduled physician visits, and to improve health-related quality of life [96]. Topics of importance for this patient population include inhaler use and technique, pursed lip breathing technique, techniques for energy conservation, self-management skills, decision making during exacerbation , end of life issues, etc. [1].

1.6.3 Pharmacotherapy

Pharmacotherapy is central to reduce symptoms and/or complications [93]. This form of treatment differs from one individual to another and is based on disease severity and frequency of exacerbations [3]. Three main types of pharmacotherapy treatments are commonly prescribed for COPD patients: bronchodilators, anti-inflammatories, and vaccines.

Bronchodilators are a class of medications which relax smooth muscle around the airways thus improving expiratory flow rates and reducing hyperinflation [3]. Three common types of bronchodilators include: β-agonists, anticholinergic drugs, and mythelxanthines [3]. Bronchodilators are normally administered through an inhaler or nebulizer [3]. Short-acting bronchodilators, such as anticholinergics (e.g., ipratropium bromide) and β_2-agonists (e.g., albuterol), have been shown to improve dyspnoea, pulmonary function, and exercise tolerance in moderate to severe COPD patients [3]. Long-acting agents (e.g., salmeterol, tiotropium) are more effective than short-acting bronchodilators [3]; indeed, greater benefits in chronic dyspnoea, pulmonary function, and health-status have been observed with the long-acting agents in this patient population [3]. Common side-effects of bronchodilators include tachycardia, heart palpitations, irritability, insomnia, muscle cramps, and tremors [3]. Methylxanthines (e.g., theophylline) are another form of bronchodilator (weaker form) which is administered orally [2, 3]. This medication offers modest improvements in dyspnoea, pulmonary function, and exercise performance compared with other bronchodilators [3]. In general, patients on this medication should be prescribed the lowest possible dose (8-14 $\mu g \cdot dL^{-1}$) due to inherent cardiovascular and neurological adverse effects [3, 41].

Anti-inflammatories, such as inhaled corticosteroids, are also commonly prescribed to patients with COPD. The use of inhaled corticosteroids unaccompanied by other medications remains a controversial issue due to conflicting effects on a multitude of outcomes such as symptoms, pulmonary function, airway inflammation, frequency and severity of exacerbations, and health status [3]. Randomized controlled trials have yet to show significant results pertaining to the improvement in lung function through the use of this medication [3]. Side-effects include ecchymosis, dysphonia, oral candidiasis, cataracts, glaucoma, pneumonia, and a decrease in bone density [3]. However, combinations medications including bronchodilators and inhaled corticosteroids have proven to be effective [2, 3, 41].

Vaccines are highly recommended for patients with COPD to prevent acute exacerbations from occurring [3]. The two most common are influenza vaccines and pneumococcal vaccines [3]. It is recommended that patients receive one influenza vaccine per year whereas pneumococcal vaccines should be administered once every 5 to 10 years [3]. It has been shown that annual influenza shots reduce morbidity and mortality by 50% in elderly patients, and reduces hospitalizations by 39% in patients with chronic lung disease [3]. The specific benefits of pneumococcal vaccines are less understood and are therefore recommended to be administered less frequently [3].

It is important to note that none of the current medications has been shown to alter the decline in lung function that occurs over time in COPD patients [93]. In addition, the effects of COPD medications on exercise tolerance, peripheral muscle function, and quality of life are modest compared to those of certain non-pharmacological interventions, such as pulmonary rehabilitation [97].

1.6.4 Oxygen Therapy

Oxygen therapy is a form of treatment carried out through the administration of supplemental oxygen in hypoxemic patients. This form of treatment benefits the patient by increasing the supply of oxygen to the lungs, thereby increasing the amount of oxygen available for the body tissues. The preferred methods to determine whether a patient requires this form of treatment are an arterial blood gas assessment (PaO_2) and surveillance of arterial oxygen saturation via pulse oximetry (SpO_2) [2]. Physiological indications for oxygen therapy include having a resting arterial oxygen partial pressure (PaO_2) < 7.3 kPa (55 mmHg) as well as an SpO_2 < 88% [2]. Concerning arterial oxygen saturation, the goal through the use of this treatment is to maintain a SpO_2 > 90% during sleep, rest, and exertion [2]. It is possible for those who are physically active to require oxygen therapy only during exercise or physical activities; in such cases, a portable oxygen tank can be used [2]. It is equally possible for patients with COPD to be prescribed oxygen therapy only during exacerbations [2]. In this case, prescription of oxygen therapy needs to be re-evaluated 30-90 days afterward by rechecking arterial blood gas [2]. Sources of oxygen include gas, liquid, and concentrator [2]. Educating patients on this form of treatment is essential and has been shown to improve compliance rates [2].

1.6.5 Surgery

Few surgical treatments are available for COPD patients. One such treatment is lung volume reduction surgery [41]. This type of surgery involves the removal of parts of the lung. By removing the diseased lung tissue, the remaining healthier tissue can have an enhanced performance [41]. Lung volume reduction surgery has been shown to

reduce hyperinflation, reduce the frequency of exacerbations, improve expiratory flow rates, increase maximal work capacity, and improve health-related quality of life [41]. This type of surgery is an expensive procedure and is only recommended for a select few [41].

In patients with very severe COPD, lung transplantation surgery has been shown to improve functional capacity and quality of life [41]. To be referred for such an intervention, patients must have the following criteria: FEV_1 < 35% predicted, PaO_2 < 7.3 – 8.0 kPa (55-60 mm Hg), $PaCO_2$ > 6.7 kPa (50 mm Hg), and secondary pulmonary hypertension [41]. Limitations for this type of surgery include shortage of donor lungs, possible complications (including death during surgery, acute rejection of donor lung, bronchiolitis obliterans), infection, and its cost (ranges from $110,000 to over $200,000 US) [41]. Individual risk factors are assessed through examination of patient history, physical examination, chest x-ray, and pulmonary function tests [41]. Surgery might be contraindicated for some patients, for example being at high risk of death due to poor lung function or experiencing an exacerbation pre-surgery [41].

1.6.6 Pulmonary Rehabilitation

Pulmonary Rehabilitation (PR), combines exercise training, patient education and psychosocial support, and is widely recognized as a cornerstone in the management of COPD [1, 6, 7, 97, 98]. In a statement from the American Thoracic Society and European Thoracic Society [46], PR was defined as *"… an evidence-based, multidisciplinary, and comprehensive intervention for patients with chronic respiratory diseases who are symptomatic and often have decreased daily life activities."* The goals

of PR are to reduce symptoms, optimize functional status, improve health-related quality of life, and reduce health care costs [99, 100]. In a meta-analysis of 23 randomized controlled trials in COPD, PR was shown to significantly reduce dyspnoea, increase exercise tolerance, and improve health-related quality of life compared with standard care [101]. Its effectiveness in reducing respiratory exacerbations [102] and hospital days [103-107] has also been reported.

Exercise training is considered the key to successful PR because it is responsible for the physiological benefits associated with this intervention [46, 103]. Exercise training has been shown to improve exercise tolerance (peak $\dot{V}O_2$), peak work rate, or endurance time to constant-load exercise) in COPD patients despite the absence of improvement in resting lung function [103]. Improvements in exercise tolerance are mediated by several physiological mechanisms, including a reduction in minute ventilation for any given work rate, a desensitization to the sensation of dyspnoea, an improvement in skeletal muscle strength and oxidative capacity [103]. In the daily life of COPD patients, these physiological adaptations translate into less dyspnoea for any given task, a greater ability to perform various daily activities, and a better health-related quality of life [103, 108]. After initial scepticism in the early 1980s [109], the therapeutic role of exercise training in COPD has now gained widespread acceptance, as evidenced by its inclusion in Canadian [46], American/European [2], and World Health Organization [41] guidelines for the management of COPD.

1.7 Exercise-Training in Pulmonary Rehabilitation: How Much Is Enough?

There is considerable variability worldwide in the way PR programs deliver their exercise component [97, 98]. This is largely attributable to the fact that the optimal exercise dose (intensity, duration, and frequency) for COPD patients has not yet been determined. As a result, the current guidelines for exercise training in PR are rather vague. In their 2006 statement on PR [98], the American Thoracic Society and European Respiratory Society made the following recommendations with regards to the exercise dose: "*A minimum of 20 sessions should be given at least three times per week to achieve physiologic benefits; twice-weekly supervised plus one unsupervised home session may also be acceptable. High-intensity exercise produces greater physiologic benefits and should be encouraged; however, low-intensity training is also effective for those patients who cannot achieve this level of intensity. […] The total effective training time should ideally exceed 30 minutes. However, for some patients, it may be difficult to achieve this target training time or intensity, even with close supervision.*" Guidelines regarding session duration are based on evidence obtained in healthy individuals [110], while recommendations for frequency of training sessions stem from clinical trials of PR versus usual care that were not designed to determine optimal training dose [111, 112]. Furthermore, the evidence favouring high-intensity over moderate- or low-intensity training in COPD patients is limited. The contention that *"high-intensity training produces greater physiologic benefits and should be encouraged"* [98] comes from one small randomized clinical trial (n = 19) from Casaburi and colleagues [113], in which the physiological effects of a high-intensity training protocol (≈ 80% of peak work rate) were compared to those of a low-intensity training protocol (≈ 50% of peak work rate). At program completion (week 8), the high-intensity protocol was found to elicit greater

physiological adaptations (reduced lactate levels and $\dot{V}_E$ for a given work rate) and larger gains in exercise tolerance, and was therefore deemed as the optimal training intensity [113]. Alternative approaches, however, have been proposed such as training at the ventilatory threshold and interval training, and are used in various parts of the world as they have been proposed to be more physiologically tolerable for COPD patients [114-121].

The ventilatory threshold is commonly described as the breakpoint in the ventilatory response to incremental exercise above which minute ventilation increases disproportionately to increments in oxygen consumption [116]. This breakpoint does not occur at the same percentage of peak capacity in all individuals, and thus needs to be determined on an individual basis with incremental exercise testing. Training at the ventilatory threshold is associated with tolerable levels of ventilation and dyspnoea, a particularly valuable feature for a patient population limited by those two factors during exercise [63, 64, 122]. The effectiveness of exercise training at the ventilatory threshold was compared to that of training at a standardized moderate intensity (50% of heart rate reserve) in 24 patients with moderate COPD [116]. Despite the fact that the mean training intensity was similar between both groups, training at the ventilatory threshold led to larger physiological adaptations (greater reductions in lactate levels, CO_2 excretion, and minute ventilation for a given workload) than training at the standardized moderate intensity [116]. This approach to training was also shown to be effective at improving muscular strength and endurance in a subsequent study conducted by the same group [123]. The chronic effects of training at the ventilatory threshold (i.e. effects of several weeks or months of training) in COPD patients are therefore promising [35,

59, 116]. However, no study to date has investigated the acute response to this training intensity.

Interval (or intermittent) training consists of alternating short bouts of maximal or high-intensity exercise with periods of rest or active recovery. Recently, a systematic review by Beauchamp et al. [124] investigated the chronic effects (range: 3-16 weeks) of interval (high interval range: 80-150% of peak wattage (Wpeak) for 20 seconds-3 minutes; low interval range: 30-75% Wpeak for 30 seconds-3 minutes) versus continuous (range: 50-80% Wpeak) training among eight randomized controlled trials, including a total of 388 COPD subjects. Results revealed comparable improvements in exercise capacity and health-related quality of life for both training modalities [124]. Interval training has thus been deemed as an alternative to continuous training for COPD patients undergoing PR [46, 124, 125]. Thus far, two studies have been published comparing the acute physiological and symptomatic responses to interval versus continuous exercise. Sabapathy et al. [115] compared single exercise bouts of continuous high-intensity training (70% of peak $\dot{V}O_2$) with interval training (1 minute at 70% of peak $\dot{V}O_2$ followed by 1 minute intervals of rest), in 10 moderate COPD subjects. Results revealed that interval exercise induced significantly lower values of $\dot{V}O_2$, carbon dioxide excretion ($\dot{V}CO_2$), $\dot{V}_E$, heart rate (HR), plasma lactate concentration, dyspnoea, and dynamic hyperinflation compared to continuous exercise [115]. Additionally, subjects were able to perform a greater total amount of work [115]. In contrast, a crossover study by Vogiatzis and colleagues [117] compared continuous (80% of Wpeak) and interval (30 seconds at 100% of Wpeak followed by 30 seconds of unloaded pedalling) exercise, in 27 severe COPD subjects. Although similar degrees of

dynamic hyperinflation were observed for both exercise intensities, interval exercise was associated with a greater total amount of work achieved [117].

1.8 Affective Valence: Definition, Measurement, and Relationship with Exercise

1.8.1 Definition

According to Ekkekakis et al., the term “affect” is defined as “the most basic component of all valenced responses (i.e. positive or negative, pleasant or unpleasant), including, but not limited to, emotions and moods.” [126] Affect is broader than an emotion, the main difference being that an emotion requires cognitive evaluation, which can generate positive or negative implications on one’s ambitions or well-being [126]. According to Lazarus et al. [127], “emotions are generated and controlled by the personal implications for well-being conveyed by relationships with the environment and comprehended through an appraisal process which draws heavily on evolved intelligence and knowledge.” In other words, individuals decide what to feel after interpreting or explaining what has happened. Moods, on the other hand, are also thought to have a cognitive origin. In comparison with emotions, moods are not responses to specific events; they are responses to how we view the world [128]. Simply stated, affect is a broader feeling than an emotion or mood. Essentially, it is the difference between a pleasant versus an unpleasant feeling.

Within exercise psychology, there has been much deliberation on how to best define affective response in relation to exercise [129]. Thus far, researchers have made use of categorical as well as dimensional approaches. Watson, Clark and Tellegen [130] declared that affect is composed of two primary dimensions termed positive affect (PA) and negative affect (NA). This would be classified as a categorical approach which

organizes affective responses into distinct categories [131]. On the other hand, the dimensional approach is “based on the assumption that affective states are interrelated and can be understood by a parsimonious set of underlying dimensions” [131]. These dimensions include PA and NA as well as high and low arousal (i.e., high and low levels of vigor). PA includes feelings such as active, enthusiastic, and alert [130]. The NA dimension reflects feelings such as anger, disgust, guilt, and fear [130]. Furthermore, several dimensions exist within PA and NA. High/low PA or high/low NA describes the level of arousal felt by the participant.

1.8.2 Measurement

The measurement of affect is a controversial issue [132]. The dilemma on whether to use a categorical measurement versus a dimensional measurement is at the heart of this controversy [132]. Current views advocate that both approaches possess advantages and limitations, which will depend on the specific research question needing to be answered [128]. Researchers interested in examining specific emotions (PA and NA) should choose a categorical approach whereas researchers wanting to examine basic affect (PA and NA as well as high and low arousal) should select a dimensional approach [133]. To date, various measurement tools have been used to measure affective response. **Table 2** presents an overview of some of these tools.

Table 2. Overview of selected self-reported measures of affect.

Reference	Measure	Construct	No. Of Items
McNair et al. [134]	POMS	Mood	65
Gauvin & Rejeski [135]	EFI	Exercise- induced feeling	12
Watson, Clark & Tellegen [136]	PANAS	Positive and Negative Affect	20
Hardy & Rejeski [137]	FS	Affective response during exercise	11
Zuckerman & Lubin [138]	MAACL	Affective response during exercise	132
Thayer [139]	AD-ACL	Various transitory arousal states	4
Kendzierski & DeCarlo [140]	PACES	Exercise enjoyment	7
Mackay et al. [141]	SACL	Stress and Arousal	20
McAuley & Courneya [142]	SEES	Exercise-induced feeling states	3
Lox et al. [143]	PAAS	Feeling state	16
Monk [144]	GVA	Global vigor and affect	8

POMS: Profile of mood states; EFI: Exercise-induced feeling inventory; PANAS: Positive and negative affect schedule; FS: Feeling scale; MAACL: Multiple affect adjective checklist; AD-ACL: Activation deactivation adjective checklist; PACES: Physical activity enjoyment scale; SACL: Stress/arousal adjective checklist; SEES: Subjective exercise experiences scale; PASS: Positive affect/sensation-seeking measure; VAS: Visual analogue scale; GVA: Global vigor and affect instrument.

1.8.3 Affective Response and its Relationship to Acute Exercise

Reviewing the literature on the exercise-affect relationship is a difficult and a challenging task [145]. Variations in methodology, mainly in the measurement of affect, definition of intensity, and the choice of exercise dose, make it difficult to formulate any direct comparisons among studies [132].

To date, a common belief has been that acute exercise is usually associated with unpleasant feelings, which might explain why few individuals exercise or adhere to an exercise program [132]. As well, in the realm of the exercise-affect relationship, a

common belief has been that exercise performed at moderate-intensities, versus low or high intensities, leads to acute positive affective responses and should therefore be prescribed to all individuals involved in an exercise program [132]. Based on these traditional assumptions, researchers have attempted to provide clarification on the mechanisms involved in the relationship between exercise intensity and adherence through the study of affective response [126]. Currently, this area of research is expanding and studies have shown that exercise intensity is negatively related to acute pleasure responses [132] and adherence [146, 147] to an exercise program.

A large extent of research has focused on the dose-response relationship between acute exercise and affect [132, 148]. This interest has been based on the notion that a specific exercise intensity and duration will elicit a certain affective response. Thus far, the common beliefs for exercise have been that moderate intensity elicits positive affective changes [149-151], low intensity is suspect to bring about any changes in affect (76-80), and high intensity is likely to be unpleasant [149-152]. However, researchers have argued that this relationship in an acute condition is possibly dependent on inter-individual differences and therefore cannot be generalized to the entire population [153]. Possible inter-individual differences suggested include; the individual's personal goals and objectives for exercising, initial aerobic fitness, the physical and social environment, how the individual perceives the exercise stimulus, as well as the psychological state of the individual [132]. Exercise duration of single bouts, on the other hand, have not been shown to have an impact on affective changes [154, 155]. Furthermore, it has been shown that affect during acute exercise is negatively correlated with physiological responses of metabolic strain, such as heart rate, respiratory rate, oxygen consumption, and blood lactate levels [156, 157].

1.8.4 Affective Response to Acute Exercise among COPD Patients

To date, few studies have looked at affective response to acute exercise training among COPD patients. A study performed by Carrieri-Kohlman et al. [158], examined whether patients with COPD at rest and during acute exercise could make the distinction between affective response to dyspnoea and perceived shortness of breath [158]. This study defined affective response as distress and anxiety experienced from dyspnoea [158]. They used several visual analogue scales to measure breathing effort, shortness of breath, as well as distress and anxiety associated with dyspnoea [158]. This study revealed that COPD patients exercising in acute conditions can, in fact, differentiate the sensation of dyspnoea from affective response [158].

Another study performed by Carrieri-Kohlman et al. [159] looked at dyspnoea and affective response during long-term exercise training in subjects with COPD. This randomized clinical trial included 45 dyspnoea-limited patients with COPD who underwent a 12-week exercise training program with and without nurse coaching [159]. The 12 week program was divided into 4 weeks of supervised treadmill training and 8 weeks of home walking [159]. This study defined affective response as simply dyspnoea-related anxiety and used a visual analogue scale and the state-trait anxiety inventory as measurement tools [159]. The objectives of the study were to compare dyspnoea intensity, dyspnoea-related anxiety, and exercise performance [159]. Results showed that dyspnoea-related anxiety rapidly decreased within the first 4 sessions despite constant levels of dyspnoea intensity [159]. Further investigation revealed that

exercise training with coaching is as effective when compared to exercise training alone in improving exercise performance, dyspnoea, anxiety, and distress [159].

In summary, evidence regarding the relationship between affect and exercise in COPD patients is scarce. Furthermore, prior investigations have used surrogate rather than direct measures of affect, such that the affective response to an acute bout of exercise in COPD patients remains unknown.

1.9 Adherence: Definition, Measurement, and Relationship with Exercise Intensity

1.9.1 Definition

In the late 1970's, the term "compliance" was used to describe the extent to which an individual's behaviour corresponds with medical or health advice from a health care professional [160-162]. Yet as time passed, a more patient centered approach to healthcare emerged and, thus, the strong need to differentiate compliance from the term "adherence" [160-162]. Adherence, according to the World Health Organization, is defined as the "the extent to which a person's behaviour - taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider" [162]. The term compliance suggests that a patient is a passive rather than an active entity in their medical treatment plan, and should patients be non-compliant to treatment recommendations by their health care provider, they are regarded as defiant [160, 162]. The term adherence is thought to better describe the patient-health care provider relationship as a partnership, and acknowledge the patient's active role in their medical treatment, and has thus been identified as the term of choice [160, 162].

1.9.2 Measurement

To quantify the effectiveness of exercise training programs used in PR, a direct and accurate measure of adherence to exercise training recommendations is necessary. No “gold standard” currently exists for measuring exercise adherence and existing methods do not allow for great precision [162]. Thus far, mostly indirect measures of adherence such as rates of participation (i.e., registration to the program or starting the program), completion (i.e., finishing the program), and attendance (i.e., number of

exercise sessions attended) have been used in COPD. Depending on the selected method, rates of adherence for exercise-training [118, 120, 121, 163-165] and PR [166-169] have shown large variability making it difficult to compare results across studies. Another concern is the lack of precision with existing methods; having attended the exercise training sessions does not guarantee adherence to the prescribed training intensity.

1.9.3 Adherence to Exercise in COPD

Since the benefits associated with exercise-training have been well established in the context of PR, adherence to current exercise recommendations has now become an important topic. In 1997, Maltais et al. [164] conducted a study investigating 42 moderate to severe COPD subjects who were instructed to cycle at a high-intensity corresponding to 80% of their Wpeak for 25 to 30 minutes, 3 times/week for 12 weeks. Oxygen supplementation was necessary during training for some subjects [164]. Intensity was adjusted on an individual basis according to subjects' level of dyspnoea, HR, fatigue, chest or leg pain, and/or dizziness [164]. Attainment of the target intensity was defined as the achievement of ≥ 80% Wpeak for the entire duration of training sessions[164]. Results revealed a mean group attendance rate of 86 ± 10% and the prescribed training intensity was attained in 0 (0%), 3 (7.1%), 5 (11.9%), and 5 (11.9%) subjects at weeks 2, 4, 10, and 12; respectively [164]. Authors concluded that high-intensity training, as defined in their study, is not well tolerated by the majority (88%) of moderate to severe COPD patients [164].

Five years later, Vogiatzis et al. [118] conducted a randomized controlled trial comparing continuous training at 50% of Wpeak to interval training with 30-second intervals at 100% of Wpeak alternated with periods of rest. Thirty-six moderate to severe COPD patients, two of which required oxygen supplementation during training, participated in a PR program, which included exercise-training sessions lasting for 40 minutes each, 2 times per week, for 12 weeks [118]. Both groups completed a similar total amount of work and had similar HR responses, however the interval training group was associated with significantly less dyspnoea [118]. Adherence, defined as the mean percent attendance, was relatively high with 90 ± 4% for the interval training group and 88 ± 4% for the continuous training group, and the difference between groups was not statistically significant [118]. However, authors stated that they specifically chose to conduct the PR program on a 2 day per week basis to ensure high attendance rates and results likely reflect this choice [118].

In 2006, Puhan et al. [121] randomly assigned 98 severe COPD patients to either 3 weeks (12 to 15 sessions) of continuous high-intensity training or interval training as part of a PR program. Subjects in the high-intensity continuous training protocol cycled at 70% of Wpeak [121]. The interval training protocol was comprised of 20-second intervals at 50% of maximum exercise capacity alternating with 40-second intervals at 10% of maximum exercise capacity [121]. According to Meyer et al. [170], 50% of maximum exercise capacity corresponds, on average, to 90% to 100% of maximal exercise capacity. Both groups were instructed to exercise for 24 minutes per session, however subjects were allowed to take breaks, if necessary [121]. Eighty-eight subjects (90%) completed the PR program. With adherence defined as having followed at least 12 exercise sessions, results revealed that subjects in the interval training protocol

adhered significantly better that those in the high-intensity training group (47.9% versus 27%; respectively) [121].

Arnardóttir and coworkers [120] subsequently investigated 60 moderate to very severe COPD patients who cycled twice per week for 12 weeks performing either interval exercise (high interval: ≥ 80% of Wpeak, low interval: 30-40% of Wpeak, interval time for high and low: 3-minutes) or continuous exercise (≥ 65% of Wpeak). Sixty percent of subjects completed the program and of these completers, the mean attendance rate was 91% with values ranging from 81% to 100% [120]. No significant between-group differences were found between groups for attendance [120]. Non-completers (40%) were identified as having a more severe disease severity [120].

Varga and colleagues [165] also compared continuous versus interval versus self-paced training to an 8-week program in 71 patients with mild to severe COPD; where subjects trained 3 times per week for 30-45 minutes each session (duration was increased during the program). The continuous group trained at 80% Wpeak, the interval group trained for 2 minutes at 90% Wpeak alternated with 1 minute intervals at 50% Wpeak, and the self-paced group was instructed to cycle, walk, or climb stairs at the same frequency and duration as the other two groups. Seventy-seven percent of individuals completed all sessions in the continuous training group, while 82% of all individuals completed all sessions in the interval training group. However, the target intensity for the interval training group could not be achieved by 24% of individuals during the initial sessions and thus the initial intensity was lowered to 70% Wpeak at the high intensity phase and 40% Wpeak at the low intensity phase for the first 9 training sessions, thus resulting in a mean attained work rate of 77% for the entire program.

Physiologic training effects were similar for continuous and interval training yet superior to self-paced training.

Finally, Mador et al. [163] included 41 moderate-to-severe COPD patients who were randomized to either continuous or interval training; where subjects trained 3 times per week for 8 weeks as part of a PR program. Both cycle ergometers and treadmills were utilized for the training modalities [163]. For the continuous group, subjects cycled continuously at 80% of Wpeak and walked on 0% incline at a speed set at 80% of the average speed attained on the 6-minute walking test [163]. Those in the interval training group, cycled for 1 minute at 150% Wpeak and 2 minutes at 75% Wpeak or walked for 1 minute at 150% and 2 minutes at 75% of the average speed attained on the 6-minute walking test [163]. In both groups, once subjects were able to exercise for 20 minutes (for continuous group) and 21 minutes (for interval group) with a Borg rating for dyspnoea and leg fatigue inferior to 5, workload was increased by 10% for cycling and 5-10% for walking [163]. Results revealed that both groups were similarly tolerable and mean attendance was 92% (range: 71% - 100%) [163].

Overall, the current literature reports mean attendance rates ranging from 86% to 92% [118, 120, 163, 164], mean completion rates ranging from 60% to 90%, and when comparing continuous versus interval training, rates of completion/adherence ranging from 11.9% to 77% and 47.9% to 82%; respectively [164, 165, 171]. A systematic review by Beauchamp et al. [124], reported similar rates of attendance and no between-group differences between continuous and interval training were found. It appears that general rates of attendance are high, yet when the definition of adherence gets more specific (such as that used in Maltais et al.), rates of adherence are lower.

1.9.4 Predictors of Non-Adherence to PR in COPD

Although several studies have investigated predictors of non-adherence to medications in COPD patients [161, 172-175], few studies have examined predictors of non-adherence to PR. To date, decreased quadriceps strength [176], being a current smoker [169, 177], increased number of smoking pack-years [176], greater degree of breathlessness [177], depression [176, 178], anxiety [178], social isolation [169], lack of social support [169], being less adherent to other healthcare activities [169], increased frequency of hospital admissions [177], increased program length [177], and increased travel time [177, 178] have all been identified as predictors of non-adherence. Using a multiple linear regression analysis, Sabit et al. [177] found that travel time, dyspnoea score, being a current smoker, program length, and number of hospital admissions in the preceding year accounted for 18% (adjusted r^2) of the variance observed in attendance. In comparison, Garrod et al. [176] found that quadriceps strength, number of pack-years, and depression together predicted 45% (adjusted r^2) of the variance observed in drop-outs versus completers [176]. Baseline characteristics, such as BMI, co-morbidity, FVC, SpO_2, 6-min walk distance, perceived dyspnoea, and score on the St-Georges Respiratory Questionnaire do not seem to predict adherence to PR [169, 177, 178]. On the other hand, better socioeconomic status and having an $FEV_1 \geq 20\%$ of the predicted normal value have been identified as baseline predictors of adherence [178]. However, to our knowledge, no studies have investigated acute exercise-response measures that predict adherence to PR in this patient population.

2. RESEARCH OBJECTIVES AND HYPOTHESES

2.1 Objectives

i) Describe and compare, in COPD patients, the acute physiological, symptomatic, and affective responses to CTHI, CTVT, and IT.

ii) Examine the nature and degree of association between acute measures of intensity and adherence to a 12-week exercise-training program to determine whether an intensity-adherence trade-off occurs in this patient population.

iii) Investigate whether the relationship between acute responses and adherence is mediated or moderated by affect/vigor.

2.2 Hypotheses

i) CTHI will induce the highest levels of $\dot{V}O_2$, $\dot{V}CO_2$, $\dot{V}_E$, HR, dynamic hyperinflation (↓IC), and dyspnoea, followed by IT and CTVT respectively. From pre- to post- exercise, affect will improve irrespective of the exercise-training protocol. During exercise, affect will remain stable or improve for CTVT, and worsen for CTHI and IT.

ii) Acute measures of exercise intensity will be negatively related to 12-week adherence. More specifically, $\dot{V}O_2$, $\dot{V}_E$ (RR being the driving force), and HR will be inversely related to 12-week adherence.

iii) Affect will mediate the relationship between acute measures of intensity and 12-week adherence.

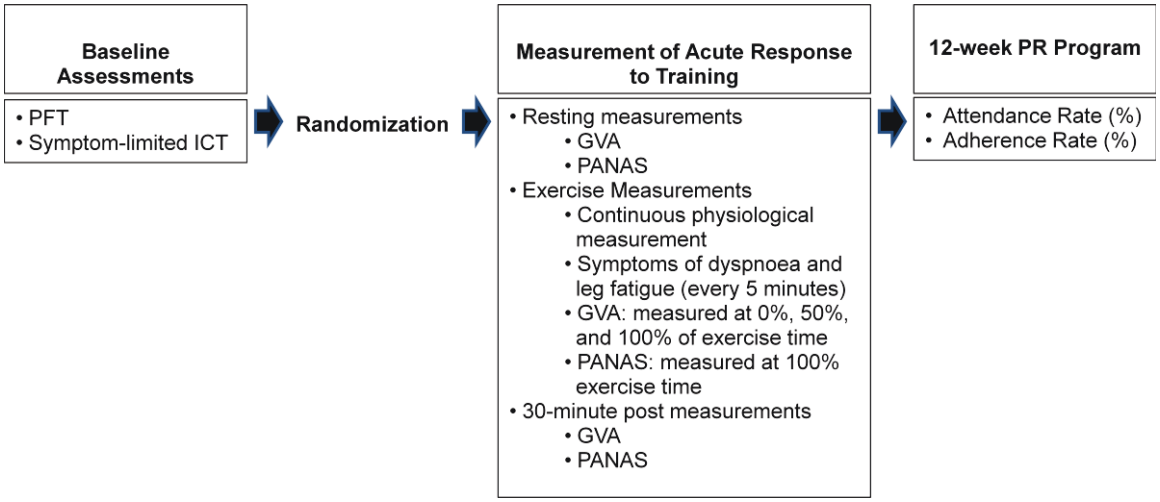
3. METHODOLOGY

3.1 Study Design and Procedure

The present project was a sub-study to a larger randomized clinical trial comparing the effects of continuous training at a high intensity (CTHI), continuous training at the ventilatory threshold (CTVT), and interval training (IT) on various PR program outcomes (clinical trial registration number: NCT01933308). CTHI was considered the standard of care since it is currently recommended by guidelines to which the alternative approaches were compared. A control group was not included in the present study design, since it would be deemed unethical to withhold PR. **Figure 5** presents an overview of the study protocol. Eligible subjects completed baseline evaluations, were randomly assigned to one of the three exercise-training protocols, were monitored during one bout of exercise training (acute response), and underwent a 12-week comprehensive PR program, where they trained 3 times/week. The PR program included exercise training, relaxation, and self-management education. The exercise-training component encompassed aerobic training according to the assigned protocol, resistance training (upper back, shoulders, chest, biceps, triceps, abdominals, quadriceps, buttocks, abductors of the thigh, and calves), and stretching (upper back, shoulders, chest, biceps, triceps, abdominals, quadriceps, buttocks, calves). During the relaxation portion of the sessions, subjects were instructed to sit or lie down for 20 minutes in a comfortable position while listening to a CD created specifically for the relaxation of COPD patients. Education/self-management training was based on *Living Well with COPD*. Sessions lasted approximately 2 hours each. The only component that differed between groups was the exercise-training intensity. Both the tributary and larger

projects were approved by the institutional ethics committee and a signed informed consent was obtained for each project separately.

Figure 5. Study overview.



PFT: Pulmonary function test; ICT: Incremental cycling test; PANAS: Positive and negative affect instrument; GVA: Global vigor and affect instrument; PR: Pulmonary rehabilitation.

3.2 Subjects

Subjects were recruited at l'Hôpital du Sacré-Coeur de Montréal according to the following eligibility criteria: *Inclusion criteria*: 1) COPD diagnosis; 2) age ≥ 40 years; 3) smoking history ≥ 10 American pack-years; 4) post-bronchodilation FEV_1 < 80% of the predicted normal value; and 5) FEV_1 to FVC ratio < 0.7. *Exclusion criteria*: 1) exacerbation of respiratory symptoms in the past 4 weeks (i.e. change in dyspnoea or volume/colour of sputum, need for antibiotic treatment, or need for hospitalization); 2) any contraindication to exercise testing [39]; 3) any active condition other than COPD that can influence exercise tolerance (unstable coronary heart disease, left congestive

heart failure, neoplasia, severe claudication, severe arthritis, etc.); 4) need for oxygen therapy at rest or during exercise; 5) participation in a PR program in the past year; 6) participation in a current exercise-training program of similar or greater dose than the protocols under study; and 7) inability to complete baseline evaluations (including the achievement of a ventilatory threshold on the incremental cycling exercise test). These criteria are mostly meant to differentiate COPD from other respiratory diseases and to ensure clinical stability and patient safety.

3.3 Baseline Assessments

Pulmonary Function Test: Expiratory flow rates, lung volumes, and lung diffusion capacity for carbon monoxide (D_LCO) were obtained according to recommended techniques [179]. Values were compared to predicted normal values from the European Community for Coal and Steel / European Respiratory Society [180].

Incremental Cycling Exercise Test: In addition, a symptom-limited incremental cycling exercise test was performed to rule out the presence of cardiovascular co-morbidities and to determine the workload at peak effort and at the ventilatory threshold for subsequent determination of exercise-training intensity. Subjects were seated on an electromagnetically braked cycle ergometer (Ergometrics 800, SensorMedics, Yorba Linda, CA) and connected to an electrocardiogram as well as to a respiratory circuit through a mouthpiece. The respiratory circuit consisted of a digital volume sensor, O_2, and CO_2 analyzers, and a mixing chamber (Vmax Encore, SensorMedics, Yorba Linda, CA). After five minutes of rest and three minutes of unloaded pedalling, the workload was increased in a stepwise manner up to the individual's maximal capacity, while

subjects were instructed to maintain a pedalling speed between 50 and 60 revolutions/minute. Each step lasted one minute and increments of 5 or 10 watts were used (5-watt increments for subjects with a previous incremental cycling test who achieved < 50 watts of their predicted peak work rate or, if no previous cycling test result was available, with an FEV_1 < 1 L; 10-watt increments for those with a previous incremental cycling test who achieved > 50 watts of their predicted work rate or, if no previous test result was available, with an FEV_1 > 1 L). The incremental cycling test is frequently used in respirology [181]. Gas exchange parameters ($\dot{V}O_2$, $\dot{V}CO_2$, RR, $\dot{V}_E$), heart rate, and SpO_2 were measured at rest and during exercise on a breath-by-breath basis. Peak workload was defined as the highest workload maintained at a pedalling speed of at least 50 revolutions/minute for a minimum of 30 seconds [39]. The ventilatory threshold was determined using the V-slope method [182]. Dyspnoea and leg fatigue were evaluated at rest and every other minute during the test using the modified 10-point Borg scale [183].

3.4 Exercise-Training Protocols

The aerobic exercise-training component was performed on cycle ergometers at the hospital's cardiopulmonary rehabilitation centre (Centre de réadaptation cardio-respiratoire Jean-Jacques-Gauthier). The three exercise-training protocols are illustrated in Figure 6. Subjects began with a 10-minute warm-up (5 minutes of unloaded pedalling followed by 5 minutes of progressively increasing loaded pedalling), were then instructed to pedal at their respective target intensity and duration, and finished with a 5-minute cool-down. CTHI consisted of pedalling for 25 minutes at the HR reached at 80% of peak work rate on the symptom-limited test; CTVT consisted of pedalling at the HR

reached at the ventilatory threshold, while IT consisted of 30-second intervals at the HR reached at 100% of peak workload interspersed with 30-second intervals of unloaded pedalling. This specific IT protocol has been successfully used by Vogiatzis et al. [117]. Session duration for CTVT and IT was adjusted for each subject using metabolic equations [184], such that the total amount of work performed was comparable to 25 minutes of CTHI. Subjects were instructed to train within ± 5 beats/minute of the target HR identified. Since heart rate response at a given submaximal workload decreases as cardiorespiratory fitness increases, this approach ensures that patients remain at the same relative training intensity throughout the program. In other words, with training, the heart becomes a stronger muscle and is able to contract more forcefully, thus increasing stroke volume. Due to the increase in stroke volume, the heart rate will decrease for the same cardiac output. A 2:1 staff-to-patient ratio for the acute response measurement and a 2:6 ratio for the PR program were respected. Instructions and feedback were standardized.

Figure 6. Exercise-training protocols.

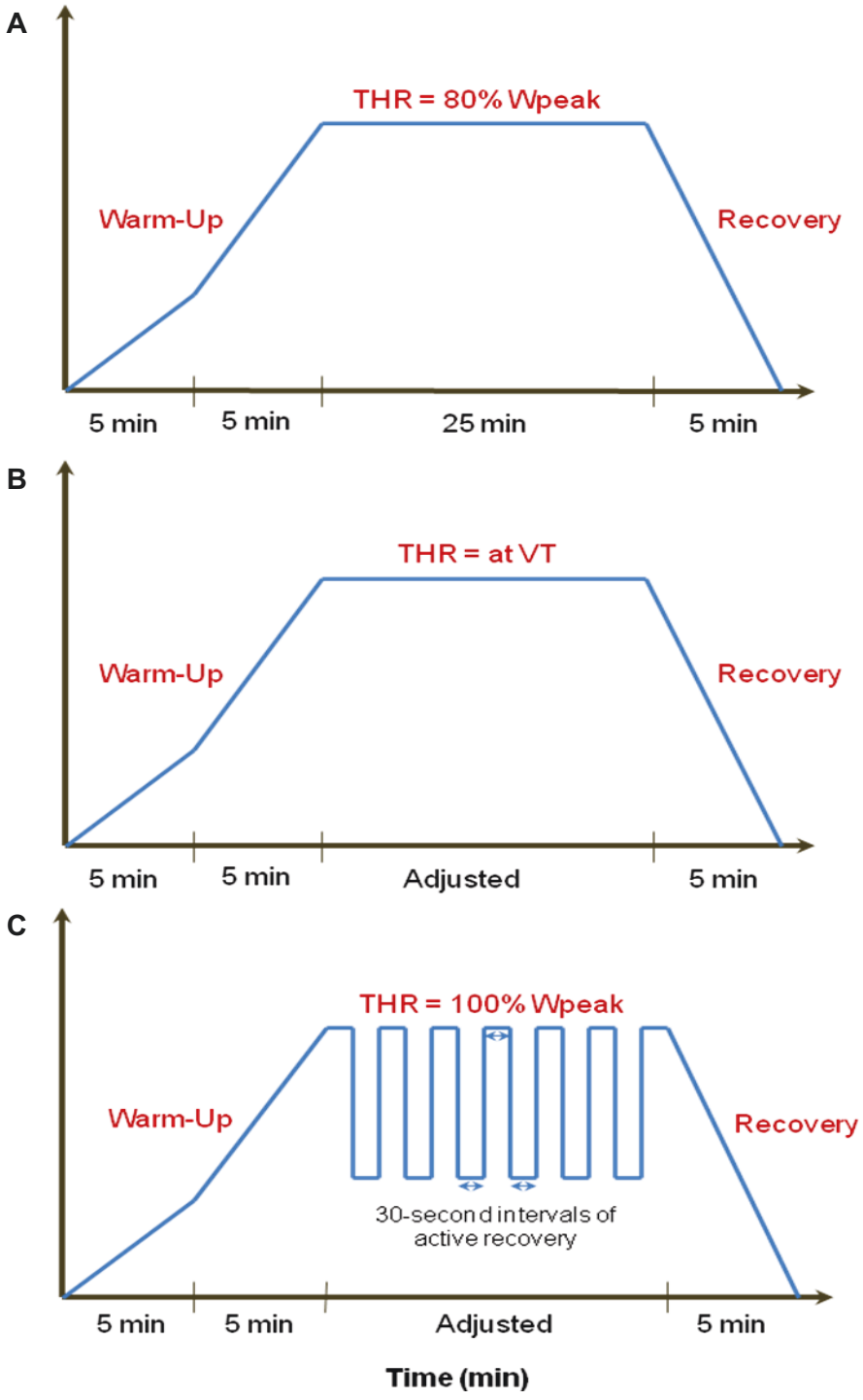


Illustration A depicts the timeline used for the CTHI protocol, illustration B depicts the timeline used for the CTVT protocol, and illustration C depicts the timeline used for the IT protocol. THR: Target heart rate; Wpeak: Peak wattage; VT: Ventilatory threshold.

3.5 Acute Response to Exercise Training

Acute response to training was measured either 1 week prior to beginning the rehabilitation program or within the first 2 weeks of program initiation (as a replacement of one of the three weekly exercise sessions). This timeframe was chosen to ensure that no physiological adaptations had taken place when the acute response was measured.

Physiological measurements, including $\dot{V}O_2$, $\dot{V}CO_2$, respiratory exchange ratio (RER), $\dot{V}_E$, V_T, respiratory rate (RR), and SpO_2 were continuously measured throughout the entire training bout using a portable metabolic system (Oxycon Mobile, Jaeger, Germany) and averaged over 30 seconds for data analysis. The portable metabolic system consists of a lightweight, battery-operated portable system mounted on the subjects' body via a vest. It records continuous data through a facemask and subsequently sends it to a host computer system through wireless transmission.
In addition, IC's as well as perceived dyspnoea and leg fatigue, as measured by the modified 10-point Borg scale [183]. More specifically for dyspnea and leg fatigue ratings, subjects were asked in French "How short of breath do you feel?" and "How much leg fatigue are you experiencing?".

Affect was operationally defined as self-reported pleasure or displeasure and measured using the Positive and Negative Affect Schedule (PANAS) and the Global Vigor and Affect (GVA) instrument. The PANAS, developed by Watson, Clark, and Tellegen [136], is a brief and easy to administer questionnaire. It consists of 20 questions related to affect, 10 dealing with positive affect (interested, excited, strong, enthusiastic, proud, alert, inspired, determined, attentive, and active), and 10 dealing

with negative affect (distressed, upset, guilty, scared, hostile, irritable, ashamed, nervous, jittery, and afraid). Next to each affective response, a table containing a five-level Likert scale ranging from "very little or not at all" to "extremely" is presented, and each level is assigned a number ranging from 1 to 5 [136]. Subjects were asked to complete the PANAS at rest, end-exercise (100% of exercise time), and 30 minutes post-exercise by circling a single number for each response indicating the extent to which they felt each affective response in that moment. Subjects were not wearing the metabolic system's face-mask at any time point that this questionnaire was administered. The scores were computed by simply adding the circled numbers associated with the positive affective responses and by adding the circled numbers associated with the negative affective responses revealing two separate scores; one for positive affect and one for negative affect. Scores range from 10 to 50 for each affective response. The PANAS's structure is consistent with the two-dimensional circumflex model and has been shown to have excellent reliability [185] and validity [136]. In addition, it has been shown to be highly internally consistent and largely uncorrelated [136]. Various time-frames have been used for the PANAS [136]; the chosen time-frame for the acute exercise bout was "in the moment".

The GVA was completed at rest, on the cycle ergometer before the subjects began pedalling (0%), halfway through the exercise bout (50%), end-exercise (100%), and 30 minutes post-exercise. During the 0%, 50%, and 100% measurements, subjects were wearing the metabolic system's face-mask. The GVA is composed of eight visual analogue scales, four related to global affect (how happy do you feel?, how calm do you feel?, how sad do you feel?, how tense do you feel?) and four related to global vigor (how alert do you feel?, how sleepy do you feel?, how much of an effort is it to do

anything?, how weary do you feel?). Each visual analogue scale is a 100 millimetre line separating opposite extremes of the mood or state of arousal [144]. Subjects were asked to place a mark on these continuums to demonstrate their overall affective state and state of arousal (or level of alertness) in that particular moment [144]. The mark placed on this continuum, ranging from 0 to 100, was then measured using a ruler. Each score was then entered into a separate equation revealing a global affect and global vigor score ranging from 0 to 100. The equations used to compute individual scores were the following:

$$\text{Global Affect} = [(\text{happy}) + (\text{calm}) + 200 - (\text{sad}) - (\text{tense})] / 4$$

and

$$\text{Global Vigor} = [(\text{alert}) + 300 - (\text{sleepy}) - (\text{effort}) - (\text{weary})] / 4$$

Visual analogue scales have an extended history in the measurement of mood [186, 187] and have been shown to be highly reliable and valid in assessing both affect and vigor [188, 189]. This measure is simple and frequently used, as shown by its inclusion in several studies assessing a wide range of subjective phenomena such as dyspnoea, pain, fatigue, sleep loss, among others [188]. Both the PANAS and GVA can be found in the Appendix.

3.6 Adherence to Exercise Training

Adherence to the exercise-training protocol was defined as the percent time spent within the target heart rate range throughout the 12-week program and was computed for attended sessions only. Achieved intensity (HR, workload in Watts and

metabolic equivalent of task (METs), estimated $\dot{V}O_2$ etc.) was monitored continuously with data tracking technology, which combines training hardware (Bike Excite Med 700, Technogym, Italy; and T31 transmitter, Polar, Finland) and software (CardioMemory, Technogym, Italy).

After each training session, a single file per subject was obtained. Each saved data file was opened in statistical analysis software and the warm-up (i.e. first 10 minutes) and cool-down (i.e. last 5 minutes) phases were eliminated to isolate the training phase of interest (i.e. where subjects were instructed to train within their target heart rate range). The data files for each subject for their entire program were then merged into a single database, thereby creating one database per subject containing all attended exercise sessions. Once created, a column was added to each individual database identifying the prescribed target heart rate for that individual. The difference between the achieved heart rate and the prescribed heart rate was then computed. This value was subsequently converted into a percentage, thus enabling us to obtain a percent adherence rate for all sessions.

Data lost due to technical difficulties were replaced by bringing the last value forward. Since subjects in the IT group were expected to spend only 50% of their time at their target heart rate (i.e. during the high interval), mean adherence for those subjects was obtained for the entire intensity phase and then multiplied by two. A detailed protocol, embedded within the manuscript entitled "Using continuous data tracking technology to study exercise adherence in pulmonary rehabilitation", can be found in the appendix.

3.7 Statistical Analyses

Baseline measurements between CTHI, CTVT, and IT were compared using one- way repeated-measures analyses of variance (ANOVA). Acute physiological and symptomatic changes during exercise training were analyzed with a series of repeated measures mixed models. To assess the acute effects of the exercise protocols on the PANAS and GVA responses, four repeated-measures general linear models were conducted (positive affect, negative affect, global affect, global vigor). To compare mean adherence between CTHI, CTVT, and IT, first, Levene's test was conducted to evaluate the homogeneity-of-variances assumption. If the assumption was met, one-way ANOVA was conducted with intervention as the between-subjects factor and adherence rate as the dependent variable. If a significant treatment effect was obtained, pairwise comparisons were conducted using Tukey's honestly significant difference (HSD) test to locate where the differences had occurred. If Levene's test rejected the assumption of homogeneity of variances, the Welch's ANOVA was used instead to test between group differences. If a significant treatment effect was obtained, the Games-Howell post-hoc test was performed to locate where the differences had occurred. To assess the intensity-adherence relationship, first, possible relationships between acute measures of intensity and adherence were identified using Partial correlations between a priori selected acute measures and 12-week adherence rates, adjusting for percent attendance rate. A priori acute measures of intensity included mean achieved workload (W), $\dot{V}O_2$ (L/min), $\dot{V}O_2$ (% peak), $\dot{V}O_2$ (% ventilatory threshold), HR (beats/min), $\dot{V}_E$ (L/min), IC / TLC, dyspnoea, leg fatigue, global affect (50% and 100%), and global vigor (50% and 100%). To ensure the absence of multicolinearity between the acute exercise measures, which avoids redundancy of correlations being conducted, correlation coefficients among variables were compared using cut-off values beyond 0.7 or -0.7

indicating the presence of multicollinearity [190]. Given our sample size, it was a priori decided that a maximum of three of the strongest correlations with adherence would be retained for further analysis. The role of global affect/vigor as potential mediators in the relationship between exercise intensity and adherence was assessed using the approach described by Preacher and Hayes, while adjusting for percent attendance rate [191]. If mediation could not be confirmed, the moderator model was tested using the approach described by Hayes, while adjusting for percent attendance rate [192]. Finally, if neither mediation nor moderation held, predictors of adherence were identified using a multiple linear regression using the strongest associations observed in the Partial correlations, while adjusting for percent attendance rate. Analyses were performed using SAS (v9.1, SAS Institute, Cary NC) and the p-value was set at 0.05.

4. RESULTS

4.1 Subjects

Baseline characteristics of the study groups are presented in **Table 3**. Thirty-five subjects completed baseline assessments and the acute training bout: 13 in the CTHI group, 12 in the CTVT group, and 10 in the IT group. The sample was predominantly composed of female participants (60%), with a mean age of 68 years (SD = 8.7), categorized in an overweight BMI category (66%). Based on pulmonary function values, participants had, on average, moderate-to-severe airflow obstruction corresponding to stage II-III COPD according to the GOLD classification [1] and significant resting lung hyperinflation (FRC > 120% predicted) and parenchymal destruction (lung diffusion capacity for carbon monoxide (D_LCO) < 60% predicted). No significant differences were found between groups at baseline, but a trend towards a lower FVC in the IT group was observed.

Table 3. Baseline characteristics of the study groups.

	CTHI (n = 13)	**CTVT** (n = 12)	**IT** (n = 10)	**p-value**
Male/Female, n	4/9	6/6	4/6	0.368
Age, years	66.3 ± 6.7	69.3 ± 8.9	66.8 ± 11.2	0.671
BMI, kg/m^2	28.3 ± 4.9	27.1 ± 5.4	28.3 ± 5.4	0.819
Smoking, pack-years	48.7 ± 17.0	47.5 ± 14.4	33.2 ± 18.1	0.159
Pulmonary Function				
FEV_1, L	1.41 ± 0.32	1.61 ± 0.42	1.28 ± 0.50	0.181
FEV_1, % predicted	59.7 ± 14.5	66.2 ± 16.7	53.8 ± 14.9	0.182
FVC, L	2.77 ± 0.59	3.20 ± 0.59	2.57 ± 0.83	0.089
FVC, % predicted	94.2 ± 15.8	105.6 ± 24.1	87.9 ± 21.6	0.136
FEV_1/FVC, %	51.9 ± 11.1	50.4 ± 9.5	49.1 ± 6.1	0.775
TLC, L	5.93 ± 1.57	6.57 ± 1.62	5.66 ± 0.85	0.311
TLC, % predicted	107.8 ± 21.9	113.0 ± 18.6	106.1 ± 15.5	0.672
FRC, L	3.93 ± 1.22	4.28 ± 1.19	3.84 ± 0.60	0.582
FRC, % predicted	131.1 ± 34.5	136.3 ± 27.5	129.9 ± 17.4	0.846
RV, L	2.96 ± 1.01	3.15 ± 1.18	2.94 ± 0.60	0.857
RV, % predicted	136.1 ± 42.3	135.8 ± 40.9	139.3 ± 33.5	0.976
D_LCO, % predicted	54.4 ± 8.1	53.1 ± 12.8	54.5 ± 10.6	0.937

Values presented are Mean ± SD. CTHI: continuous training at a high intensity; CTVT: continuous training at the ventilatory threshold; IT: interval training; BMI: body mass index; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; TLC: total lung capacity; FRC: functional residual capacity; RV: residual volume; D_LCO: lung diffusion capacity for carbon monoxide.

The response to the symptom-limited incremental cycling test for the CTHI, CTVT, and IT groups are presented in **Table 4**. As expected, our sample population had a reduced peak wattage, HR, and $\dot{V}O_2$ compared to normal predicted values [193], but nonetheless a relatively preserved exercise tolerance for a COPD population [39]. No significant between-group differences were observed, except for peak $\dot{V}_E$ / MVV, which

was significantly higher in the IT group than in the CTVT group, suggesting that the IT group was either significantly more ventilatory limited or closer to maximal effort than those in the CTVT group.

Table 4. Responses to symptom-limited incremental cycling test for each group.

	CTHI (n = 13)	**CTVT** (n = 12)	**IT** (n = 10)	**p-value**
Peak Responses				
Workload, W	65.8 ± 15.5	72.1 ± 24.8	69.0 ± 28.0	0.789
Workload, % predicted	59.6 ± 18.4	59.7 ± 15.9	62.9 ± 25.9	0.913
HR, beats/min	117.9 ± 16.7	123.1 ± 19.1	124.5 ± 18.1	0.645
HR, % predicted	77.5 ± 11.4	80.8 ± 11.7	80.8 ± 10.3	0.704
$\dot{V}O_2$, L/min	1.02 ± 0.19	1.07 ± 0.40	1.13 ± 0.39	0.738
$\dot{V}O_2$, ml/kg/min	13.43 ± 2.92	14.03 ± 3.75	14.83 ± 3.16	0.606
$\dot{V}O_2$, % predicted	80.4 ± 32.6	74.6 ± 28.8	86.2 ± 28.3	0.671
$\dot{V}CO_2$, L/min	1.07 ± 0.25	1.11 ± 0.39	1.22 ± 0.48	0.623
RER	1.05 ± 0.10	1.04 ± 0.05	1.07 ± 0.12	0.743
RR, breaths/min	33.3 ± 5.9	32.7 ± 5.1	34.6 ± 3.5	0.665
$\dot{V}_E$, L/min	40.36 ± 7.19	41.81 ± 14.13	41.63 ± 14.42	0.949
$\dot{V}_E$ / MVV	0.85 ± 0.19	0.75 ± 0.18	0.95 ± 0.13	**0.033**
SpO_2, %	94.9 ± 2.9	93.7 ± 2.2	94.2 ± 2.2	0.474
Dyspnoea, Borg	7.0 ± 2.1	6.4 ± 2.0	7.9 ± 1.9	0.236
Leg fatigue, Borg	7.8 ± 1.8	6.7 ± 2.3	7.8 ± 2.3	0.332
Responses at the VT				
Workload at VT, W	33.9 ± 18.3	37.5 ± 9.4	33.0 ± 20.6	0.788
Workload at VT, % peak	51.9 ± 27.6	54.4 ± 11.8	48.7 ± 26.4	0.848
HR at VT, beats/min	99.8 ± 13.7	100.7 ± 12.8	103.7 ± 9.5	0.740
HR at VT, % peak	83.9 ± 7.0	82.6 ± 8.6	84.3 ± 9.1	0.874
$\dot{V}O_2$ at VT, L/min	0.72 ± 0.14	0.74 ± 0.20	0.79 ± 0.19	0.658
$\dot{V}O_2$ at VT, ml/kg/min	9.42 ± 1.67	9.80 ± 1.98	10.60 ± 2.66	0.408
$\dot{V}O_2$ at VT, % peak	71.5 ± 12.7	71.8 ± 9.9	71.6 ± 8.6	0.998

$\dot{V}CO_2$ at VT, L/min	0.63 ± 0.12	0.66 ± 0.14	0.71 ± 0.17	0.469
$\dot{V}CO_2$ at VT, % peak	61.2 ± 15.9	62.0 ± 10.8	61.0 ± 10.9	0.983
RER at VT	0.88 ± 0.10	0.82 ± 0.27	0.90 ± 0.07	0.556
RR at VT, breaths/min	24.0 ± 4.4	23.5 ± 7.5	27.6 ± 3.2	0.183
RR at VT, % peak	73.9 ± 16.0	72.3 ± 20.3	80.1 ± 8.3	0.503
$\dot{V}_E$ at VT, L/min	24.80 ± 5.00	25.92 ± 7.58	27.86 ± 5.98	0.513
$\dot{V}_E$ at VT, % peak	63.5 ± 17.3	63.2 ± 9.8	70.9 ± 16.4	0.409
SpO_2 at VT, %	95.2 ± 1.9	94.4 ± 1.8	94.8 ± 1.9	0.520
SpO_2 at VT, % peak	100.4 ± 2.4	100.8 ± 1.6	100.6 ± 1.1	0.874

Values presented are Mean ± SD. CTHT: continuous training at a high intensity; CTVT: continuous training at the ventilatory threshold; IT: interval training; VT: ventilatory threshold; HR: heart rate; $\dot{V}O_2$: oxygen uptake; $\dot{V}CO_2$: carbon dioxide excretion; RR: respiratory rate; $\dot{V}_E$: minute ventilation; MVV: maximal voluntary ventilation; RER: respiratory exchange ratio; SpO_2: pulse oxygen saturation.

4.2 Acute Response to Exercise Training

The target and achieved intensity and duration during the acute exercise-training bout are presented in **Table 5**. Everyone, with the exception of one subject from the CTHI group, achieved the target exercise duration during the acute bout of exercise. **Figure 7** illustrates the time course for physiological parameters expressed in absolute values. Significant between-group differences were obtained for absolute values of $\dot{V}O_2$ (in L/min: F = 3.69, p = 0.03; in ml/kg/min: F = 3.75, p = 0.02), $\dot{V}CO_2$ (F = 5.15, p = 0.006), RER (F = 4.54, p = 0.01), $\dot{V}_E$ / MVV (F = 9.15, p < 0.001), RR (F = 10.98, p < 0.001), and IC (F = 3.28, p = 0.04). No significant between-group differences were found for HR, SpO_2, $\dot{V}_E$, V_T, and IC/TLC expressed in absolute values. **Figure 8** illustrates the time course for physiological parameters expressed in relative terms (% peak or % rest). When selected variables were expressed as a percentage of the peak attained on the

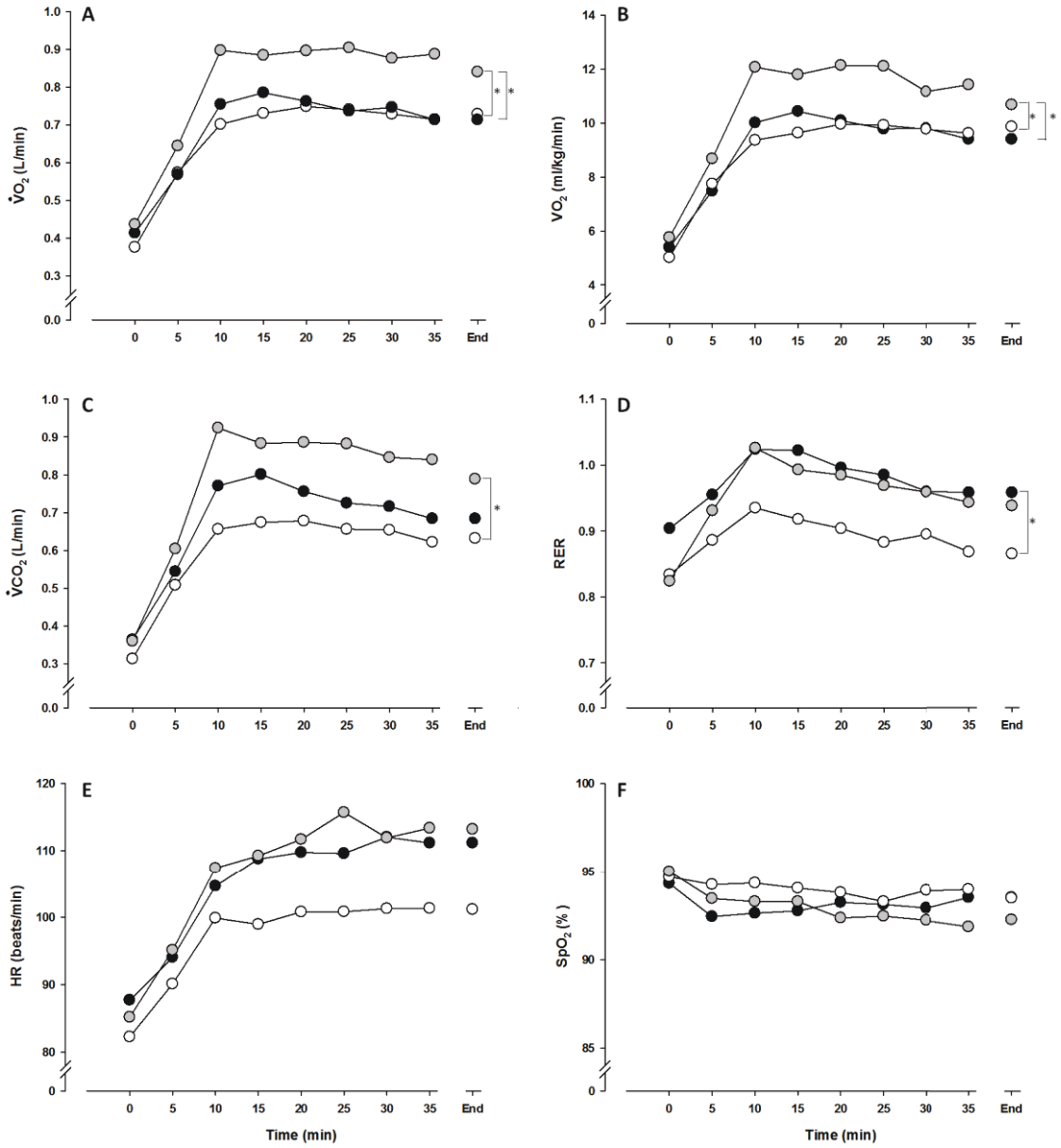
symptom-limited cycling exercise test, significant between-group differences were obtained for RER ($F = 4.23$, $p = 0.02$), HR ($F = 8.05$, $p < 0.001$), $\dot{V}_E$ ($F = 3.35$, $p = 0.04$), $\dot{V}_E$ / MVV ($F = 3.35$, $p = 0.04$), and RR ($F = 9.00$, $p < 0.001$); no significant between-group differences were found for $\dot{V}O_2$, $\dot{V}CO_2$, and V_T expressed in relative values. When selected variables were expressed as a percentage of the resting value, significant between-group differences were obtained for SpO_2 ($F = 4.89$, $p = 0.008$), whereas no differences were found for IC and IC/TLC. Based on relative values, which account for individual and between-group differences in baseline exercise tolerance, CTVT was associated with less physiological strain (lower values of RER, HR, and RR) compared to CTHI, while IT was associated with a more pronounced ventilatory response (higher values of $\dot{V}_E$, $\dot{V}_E$ / MVV, and RR) and greater drop in SpO_2 from rest.

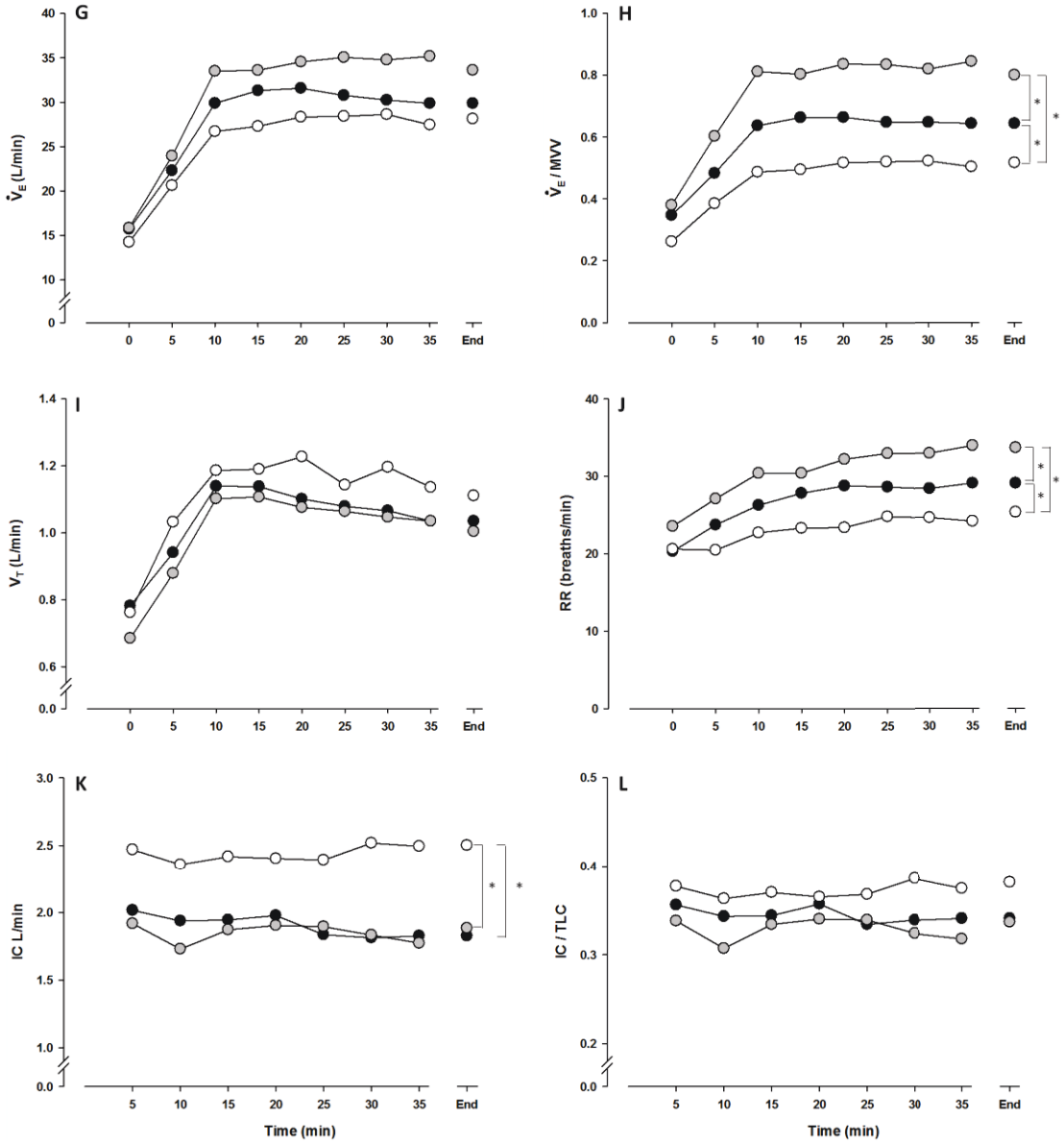
Table 5. Target and achieved response to acute exercise bout during the intensity phase of training for CTHI, CTVT, and IT.

	CTHI (n = 13)	**CTVT** (n = 12)	**IT** (n = 10)	**p-value**
Target				
Duration, min	25.0 ± 0	30.7 ± 2.9	31.5 ± 1.2	**< 0.001**
HR, bpm	109.1 ± 15.2	101.5 ± 12.2	125.2 ± 13.5*	**0.001**
Achieved				
Duration, min	24.2 ± 2.8	30.7 ± 2.9	31.5 ± 1.2	**< 0.001**
HR, bpm	109.0 ± 16.2	101.3 ± 11.4	112.2 ± 14.5**	0.187
HR, % target	99.9 ± 3.5	99.8 ± 2.4	89.6 ± 7.2**	**< 0.001**
HR, % peak	91.4 ± 4.8	83.1 ± 7.3	90.6 ± 7.9	**0.008**
HR, % VT	109.3 ± 7.0	100.8 ± 2.9	108.0 ± 7.4	**0.003**

Values presented are mean ± SD.
CTHI: continuous training at a high intensity; CTVT: continuous training at the ventilatory threshold; IT: interval training; HR: heart rate; VT: ventilatory threshold.
***** = target for the high interval (no specific target for the low interval)
****** = average of high and low interval
[#] = analyzed in 34 individuals

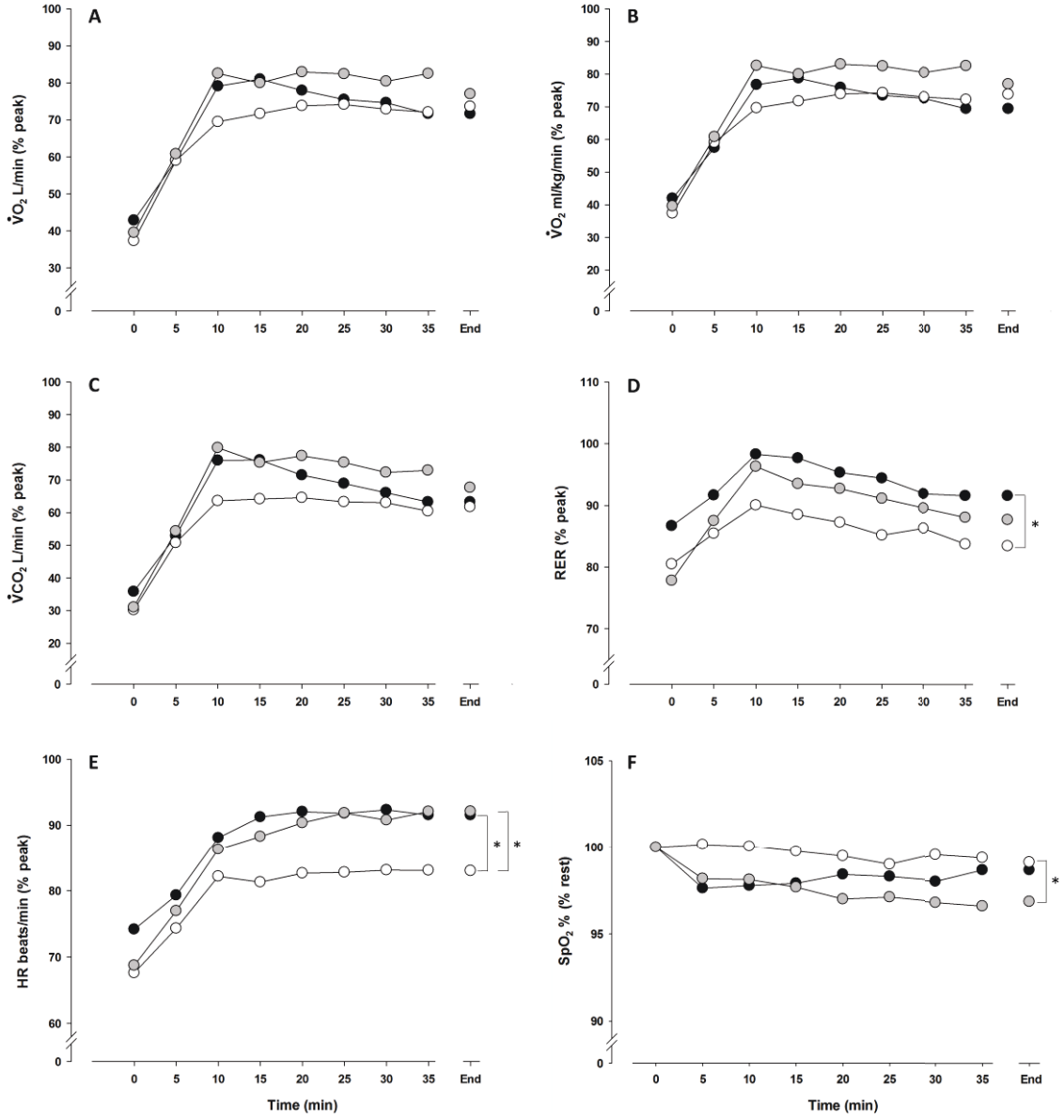
Figure 7. Time course for acute physiological parameters in absolute terms.

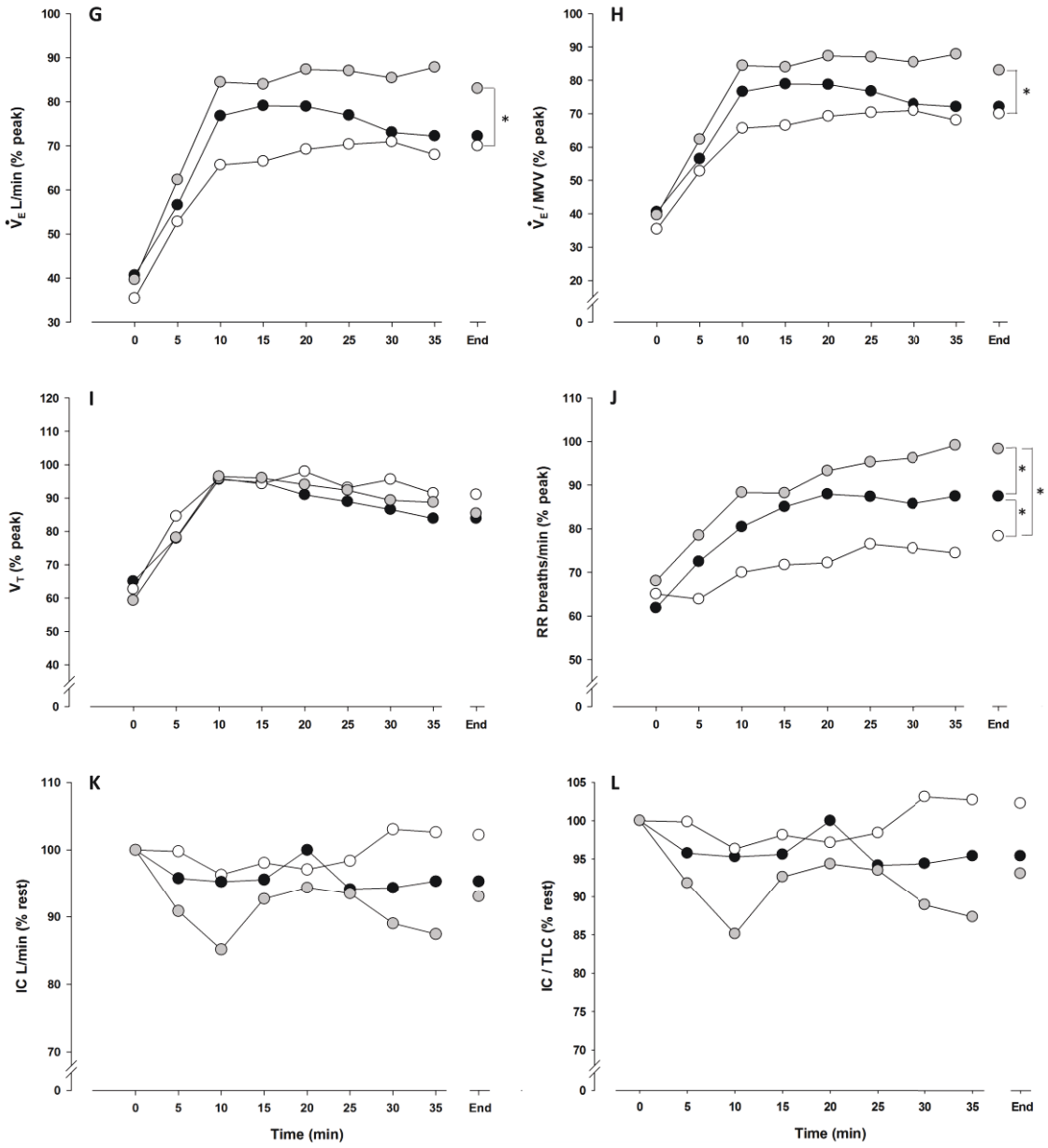




Time course values in absolute terms for $\dot{V}O_2$ in L/min (A), $\dot{V}O_2$ in ml/kg/min (B), $\dot{V}CO_2$ (C), RER (D), HR (E), SpO_2 (F), $\dot{V}_E$ (G), $\dot{V}_E$ / MVV (H), V_T (I), RR (J), IC (K), IC/TLC (L) for CTHI (black circles), CTVT (white circles), and IT (grey circles). Depicted timescales include 10-minute warm-up. Achieved values for the IT group represent the average of the high and low intervals. Values are mean. * = significant between-group difference $p < 0.05$.

Figure 8. Time course for acute physiological parameters in relative terms.

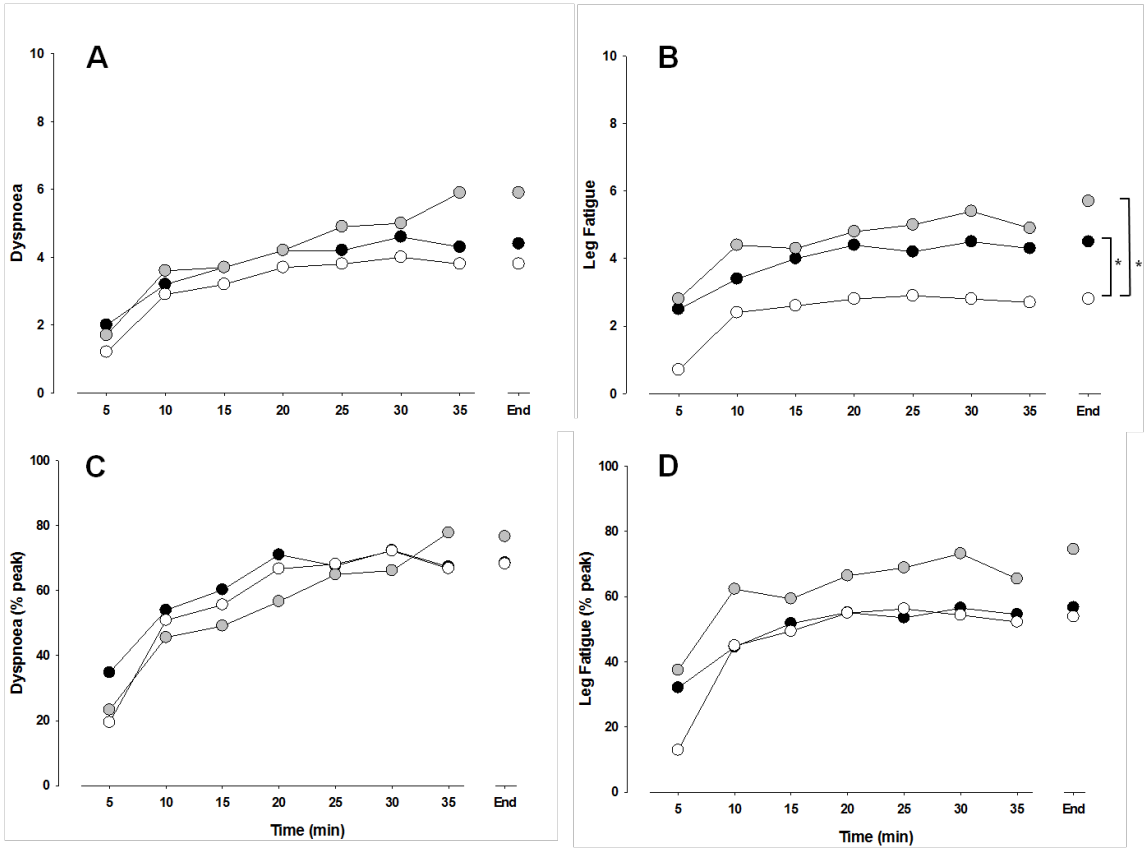




Time course values in relative terms for $\dot{V}O_2$ in L/min (% peak) (A), $\dot{V}O_2$ in ml/kg/min (% peak) (B), $\dot{V}CO_2$ (% peak) (C), RER (% peak) (D), HR (% peak) (E), SpO_2 (% rest) (F), $\dot{V}_E$ (% peak) (G), $\dot{V}_E$ / MVV (ratio of the peak) (H), V_T (% peak) (I), RR (% peak) (J), IC (% rest) (K), IC/TLC (% rest) (L) for CTHI (black circles), CTVT (white circles), and IT (grey circles). Depicted timescales include 10-minute warm-up. Achieved values for the IT group represent the average of the high and low intervals. Values are mean. * = significant between-group difference $p < 0.05$.

Symptomatic responses to the acute exercise bout are shown in **Figure 9**. The perceived level of dyspnoea was comparable between groups when expressed in absolute terms and as a percentage of the peak. An intervention effect was observed for leg fatigue, expressed in absolute terms, where subjects in the CTVT group perceived less leg fatigue throughout the exercise bout compared to subjects in the CTHI and IT groups ($F = 4.37$, $p = 0.01$). However, when expressed as a percentage of the peak, no significant between-group difference was observed.

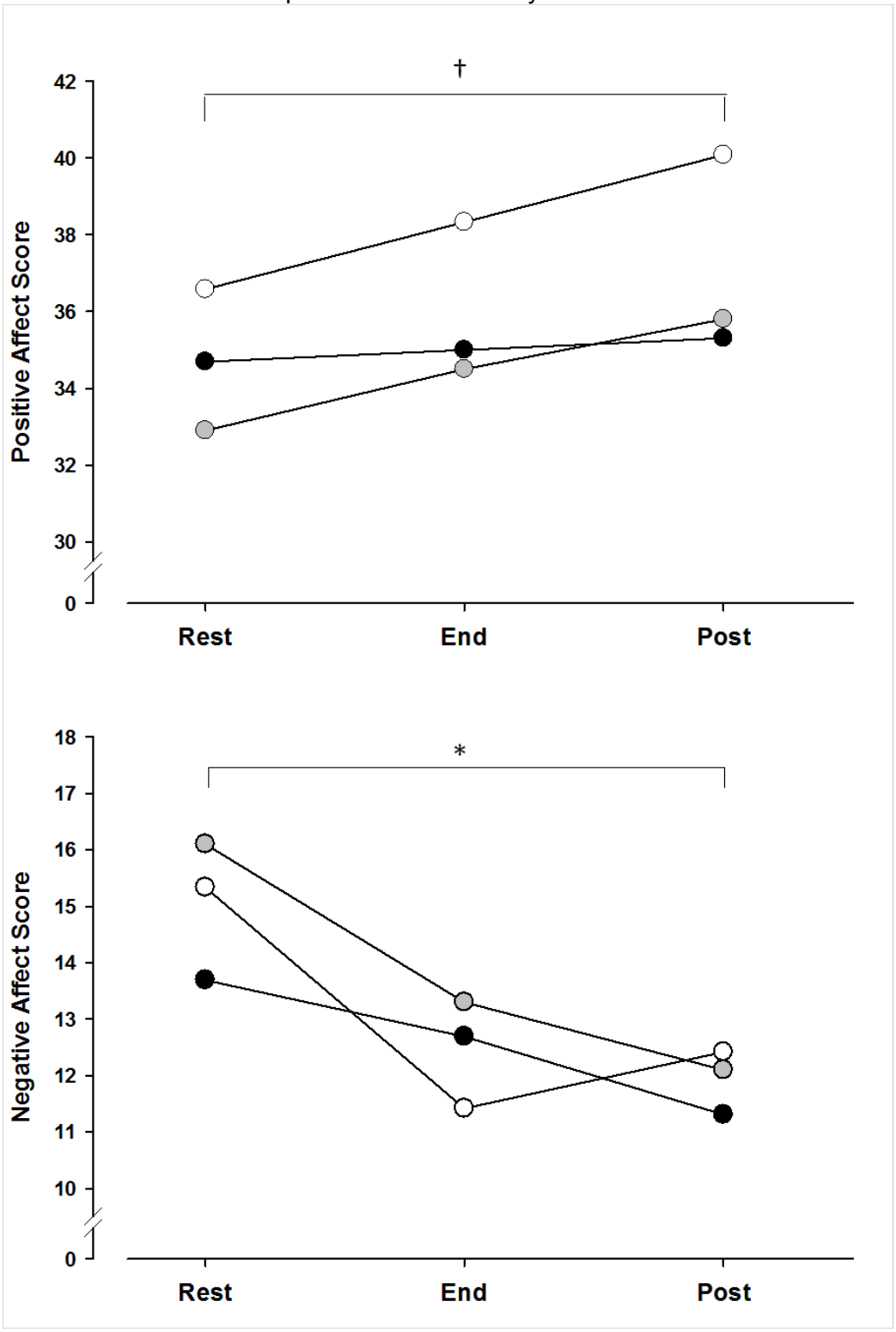
Figure 9. Acute symptomatic responses.



Dyspnoea and leg fatigue as measured by the modified 10-Point Borg scale in absolute terms (A and B) and expressed as a percent peak (C and D) for CTHI (black circles), CTVT (white circles), and IT (grey circles). Depicted timescales begin with the first 5 minute Borg measurement. Values are mean. * = significant between-group difference $p < 0.05$.

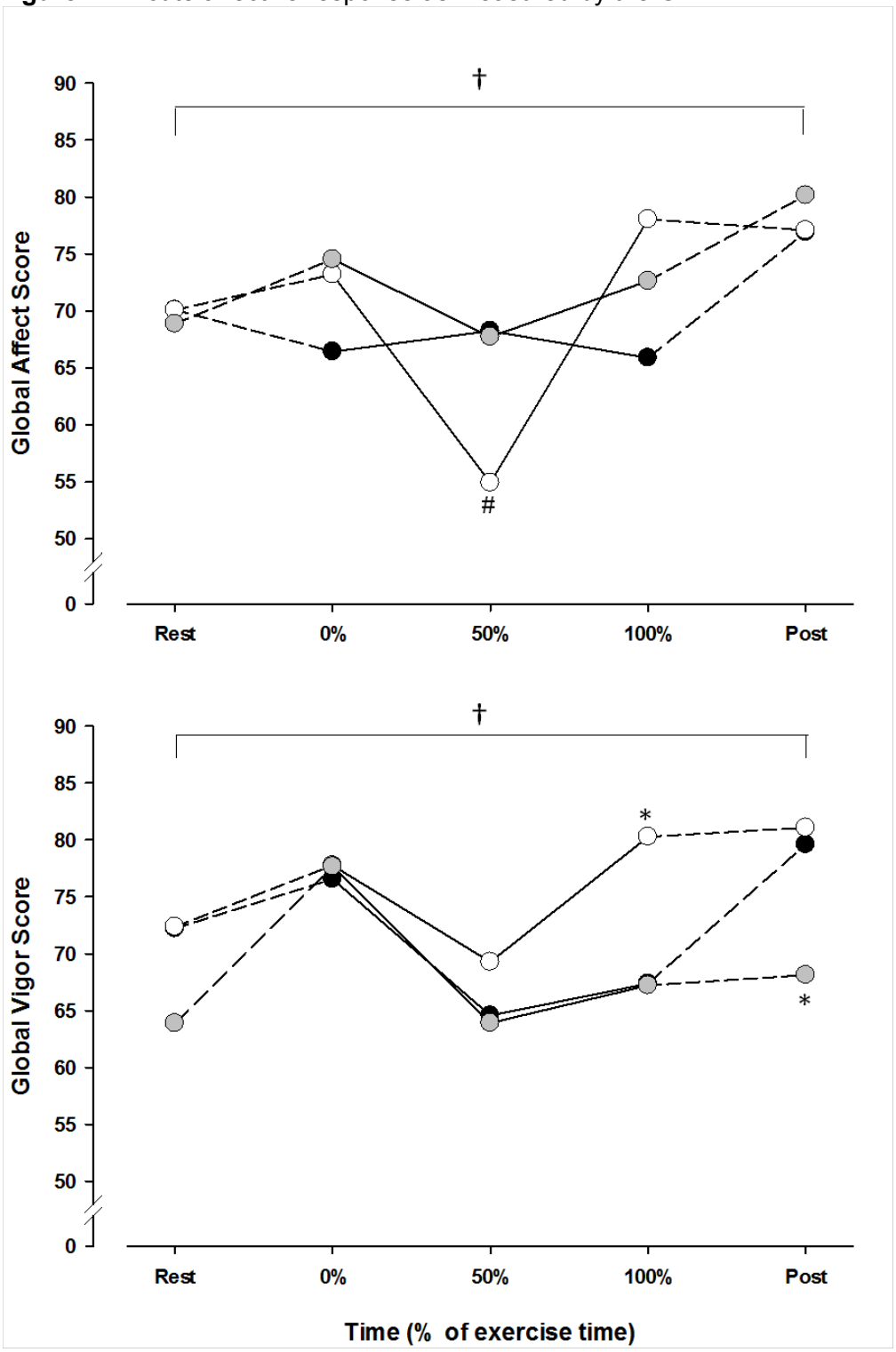
Results from the PANAS revealed a significant time effect from rest to post-exercise for positive ($F = 9.74$, $p < 0.001$) and negative ($F = 6.43$, $p = 0.005$) affect scores, but no time by intervention interaction. As shown in **Figure 10**, positive affect generally increased and negative affect generally decreased from rest to post-exercise. Results from the GVA revealed a significant time effect from rest to post-exercise for global affect ($F = 8.47$, $p < 0.001$) and global vigor ($F = 9.79$, $p < 0.001$). **Figure 11** illustrates that both global affect and global vigor generally improved from rest to 30 minutes post-exercise. Additionally, a time by intervention interaction for both global affect ($F = 2.21$, $p = 0.04$) and global vigor ($F = 2.20$, $p = 0.04$) was observed. For global affect, the CTVT group scored less than the other groups at 50% of exercise time; the difference was significant against CTHI ($p = 0.04$) and approached significance against IT ($p = 0.06$). For global vigor, the CTVT group scored significantly higher than the CTHI ($p = 0.01$) and IT ($p = 0.02$) groups at 100% of exercise time, while the IT group scored significantly less than the CTHI ($p = 0.04$) and CTVT ($p = 0.02$) groups 30-minutes post-exercise.

Figure 10. Acute affective response as measured by the PANAS.



Positive and negative affect, as measured by the PANAS, for CTHI (black circles), CTVT (white circles), and IT (grey circles). Circles represent group means. * = $p < 0.05$, † = $p < 0.001$.

Figure 11. Acute affective response as measured by the GVA.

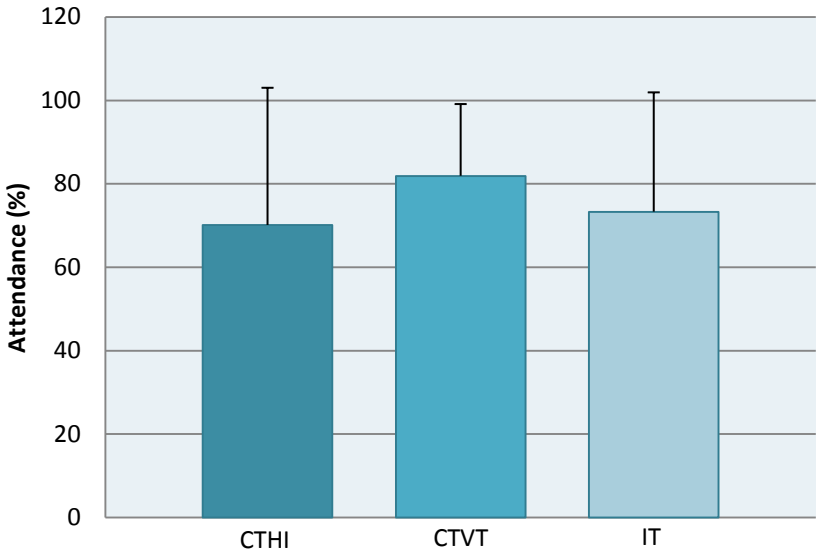


Global affect and global vigor, as measured by the GVA, for CTHI (black circles), CTVT (white circles), and IT (grey circles). Circles represent group means. † = $p < 0.001$. # = significantly different from IT and approached significance with CTHI $p < 0.05$. * = significantly different from other two groups $p < 0.05$.

4.3 Adherence to Exercise Training

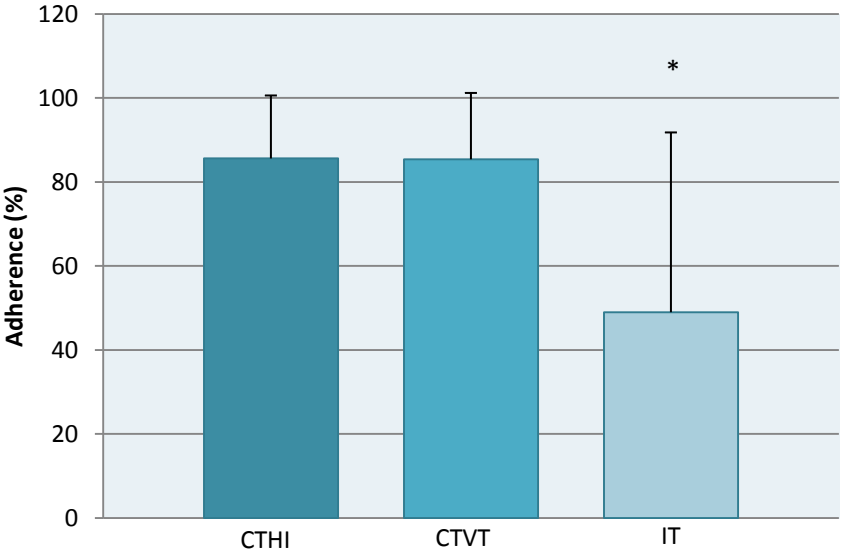
Attendance and adherence data was obtained in 34 of the 35 subjects included initially, as one subject from the CTHI group was excluded after completing the acute training bout for medical reasons. Mean attendance and adherence rates for CTHI, CTVT, and IT are illustrated in **Figures 12 and 13**, respectively. Mean attendance was 70.1 ± 32.9% (range: 49.3-91.0) for CTHI, 81.9 ± 17.2% (range: 71.0-92.9) for CTVT, and 73.3 ± 28.6% (range: 52.9-93.8) for IT. No significant between-group differences were observed for attendance. Mean adherence to the target HR throughout the 12-week program was 85.6 ± 15.0% (range: 76.0-95.1) for CTHI, 85.4 ± 15.8% (range: 75.3-95.5) for CTVT, and 49.0 ± 42.8% (range: 18.4-79.7) for IT. The adherence rate was significantly lower in the IT group compared to the other two groups ($F = 6.69$, $p = 0.004$). Box plots for attendance and adherence data are shown in **Figure 14** and **Figure 15**, respectively. Due to data not being normally distributed, measures were taken to standardize values (z-score approach, root square approach, reciprocal transformation approach, and log approach); however, standardization did not help to normalize the attendance or adherence data. Unstandardized values were thus used for subsequent analyses.

Figure 12. Mean attendance rates for CTHI, CTVT, and IT.



Mean attendance rates for CTHI, CTVT, and IT, expressed as a percentage of attended sessions over the total number of sessions offered. CTHI: continuous training at a high intensity; CTVT: continuous training at the ventilatory threshold; IT: interval training.

Figure 13. Mean adherence rates for CTHI, CTVT, and IT.



Mean adherence rates for CTHI, CTVT, and IT, expressed as a percentage of time spent within the target heart rate range throughout the 12-week program. CTHT: continuous training at a high intensity; CTVT: continuous training at the ventilatory threshold; IT: interval training. * = significantly different from CTHI and CTVT at $p < 0.05$.

Figure 14. Box plot for attendance data.

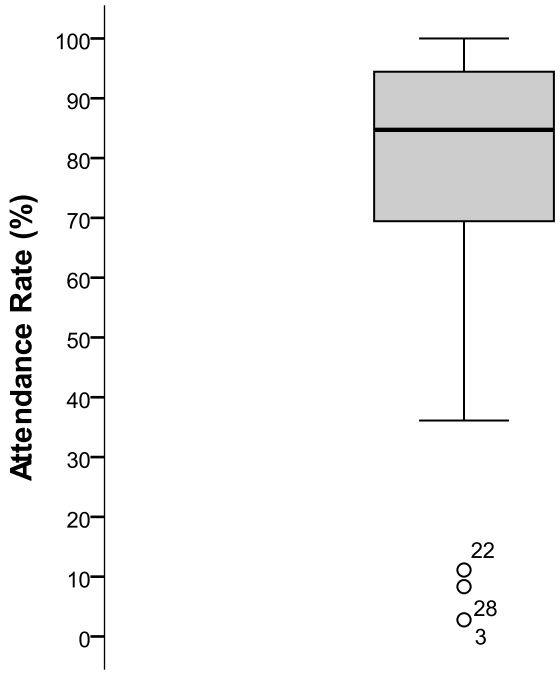
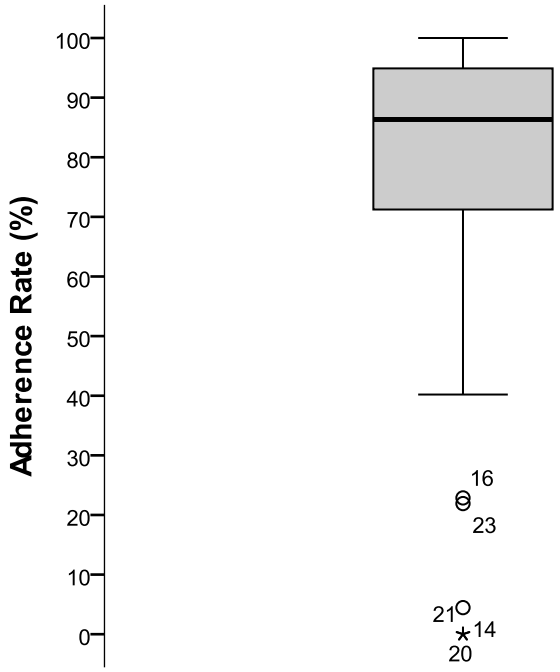


Figure 15. Box plot for adherence data.



4.4 Relationship Between Acute Response and Adherence

Results from the Partial correlation analyses between measures of acute response and 12-week adherence to training are shown in **Table 6**. After adjusting for attendance rate, mean achieved workload (W) (r = -0.429, p = 0.014), $\dot{V}O_2$ (L/min) (r = -0.466, p = 0.007), $\dot{V}_E$ (L/min) (r = -0.463, p = 0.008), and global vigor at 100% of exercise time (r = 0.420, p = 0.017) were most strongly correlated with adherence. Using the cut-off values of 0.7 and -0.7, multicolinearity was found between $\dot{V}O_2$ (L/min) and $\dot{V}_E$ (L/min) (r = 0.771, p < 0.001) and between $\dot{V}O_2$ (L/min) and Workload (W) (r = 0.832, p < 0.001). Therefore, the variables retained as the strongest correlates of adherence were mean $\dot{V}O_2$ (L/min) at the target intensity, and global vigor at 100% of exercise time.

Table 6. Results of partial correlation analysis between measures of acute responses and 12-week adherence.

Table 6. Results of partial correlation analysis between measures of acute responses and 12-week adherence.

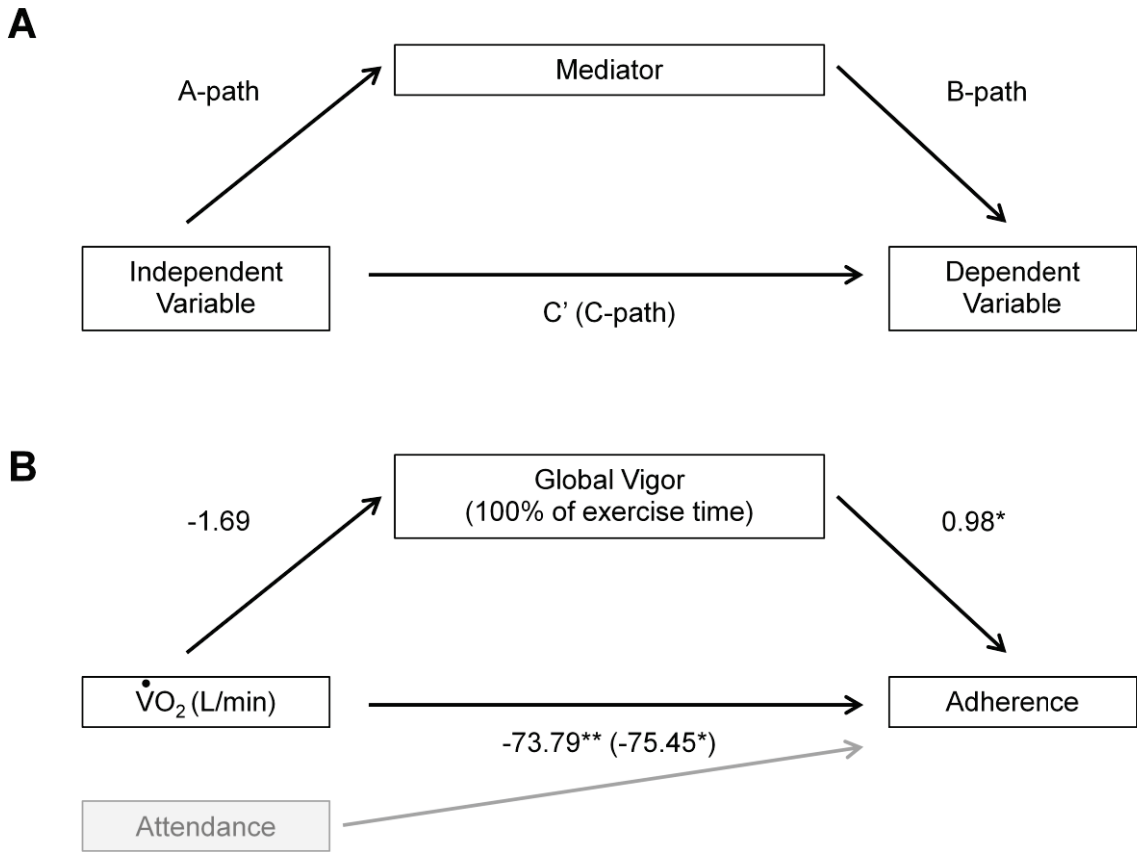
Control Variables: Attendance (%)		Workload (Watts)	VO2 (L/min)	VO2 (% peak)	VO2 (% VT)	HR (beats/mi	VE (L/min)	IC / TLC	Dyspnoea	Leg Fatigue	GA (50%)	GA (100%)	GV (50%)	GV (100%)	Adherence (%)
Workload (Watts)	Correlation	1.000	.832	-.166	.263	.097	.723	.252	-.224	.049	.039	.286	.245	.034	-.429
	Sig. (2-tailed)	.	.000	.363	.147	.596	.000	.164	.217	.791	.834	.112	.177	.855	.014
VO2 (L/min)	Correlation		1.000	.044	.320	.123	.771	.160	-.175	.080	-.029	.204	.221	-.061	-.466
	Sig. (2-tailed)		.	.811	.074	.504	.000	.382	.339	.663	.875	.264	.225	.741	.007
VO2 (% peak)	Correlation			1.000	.726	-.121	.282	-.215	.438	.354	-.011	-.265	-.263	-.138	-.102
	Sig. (2-tailed)			.	.000	.509	.117	.237	.012	.047	.952	.143	.146	.451	.579
VO2 (% VT)	Correlation				1.000	.074	.482	-.155	.458	.428	-.028	-.326	-.171	-.132	-.165
	Sig. (2-tailed)				.	.686	.005	.396	.008	.015	.880	.069	.349	.470	.367
HR (beats/min)	Correlation					1.000	.097	.280	-.070	-.164	-.148	-.023	.018	.072	-.011
	Sig. (2-tailed)					.	.597	.121	.704	.371	.419	.899	.924	.697	.951
VE (L/min)	Correlation						1.000	.195	-.010	.251	-.003	.050	.062	-.114	-.463
	Sig. (2-tailed)						.	.285	.956	.165	.988	.787	.734	.535	.008
IC / TLC	Correlation							1.000	-.135	-.147	-.521	.152	.128	.120	.095
	Sig. (2-tailed)							.	.462	.423	.002	.408	.483	.515	.605
Dyspnoea	Correlation								1.000	.684	-.147	-.474	-.372	-.161	-.122
	Sig. (2-tailed)								.	.000	.423	.006	.036	.377	.505
Leg Fatigue	Correlation									1.000	.047	-.391	-.359	-.478	-.311
	Sig. (2-tailed)									.	.799	.027	.044	.006	.083
GA (50%)	Correlation										1.000	.308	.248	-.027	-.143
	Sig. (2-tailed)										.	.087	.171	.883	.435
GA (100%)	Correlation											1.000	.621	.602	.021
	Sig. (2-tailed)											.	.000	.000	.908
GV (50%)	Correlation												1.000	.725	.259
	Sig. (2-tailed)												.	.000	.152
GV (100%)	Correlation													1.000	.420
	Sig. (2-tailed)													.	.017
Adherence (%)	Correlation														1.000
	Sig. (2-tailed)														.

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

The mediation model was tested with mean $\dot{V}O_2$ (L/mi) at the target intensity as the independent variable, global vigor at 100% of exercise time as the mediator, and adherence as the dependent variable, as presented in **Figure 16**. $\dot{V}O_2$ was negatively associated with adherence (β = -75.45, t (32) = -2.58, p = 0.02) and with global vigor at end-exercise (β = -1.69, t (32) = -0.12, p = 0.91). Global vigor at end-exercise, being the mediator, was positively associated with adherence (β = 0.98, t (32) = 2.93, p < 0.01). The 95% confidence interval for the indirect effect was obtained using 10 000 bootstrap re-samples. Results of the mediation analysis revealed that the mediating role of global vigor at end-exercise between acute $\dot{V}O_2$ and 12-week adherence could not be confirmed as the confidence interval contained zero (β = 0.28, CI = -30.56 to 37.83).

Figure 16. Tested mediation model.

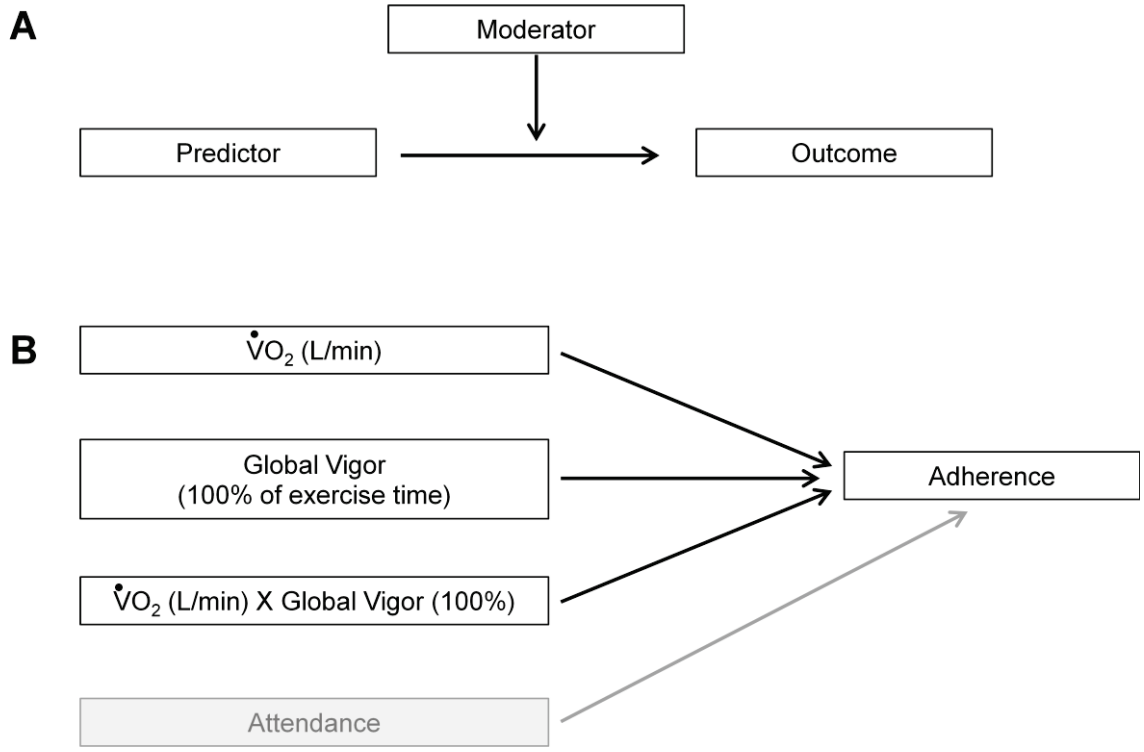


Conceptual mediation model (A) and statistical mediation model (B) with $\dot{V}O_2$ as the independent variable, global vigor at end-exercise as the mediator, and adherence as the dependent variable while adjusting for attendance. β values are shown in figure. * $p < 0.05$, ** $p < 0.01$.

The tested moderation model is presented in **Figure 17**. Moderation was tested with $\dot{V}O_2$ as the predictor (i.e. independent variable), global vigor at 100% of exercise time as the moderator, and adherence as the outcome (i.e. dependent variable). Results revealed that the product of $\dot{V}O_2$ and global vigor at 100% of exercise time was statistically significant ($\beta = 2.74$, $t(32) = 2.32$, $p = 0.03$) indicating that global vigor is a

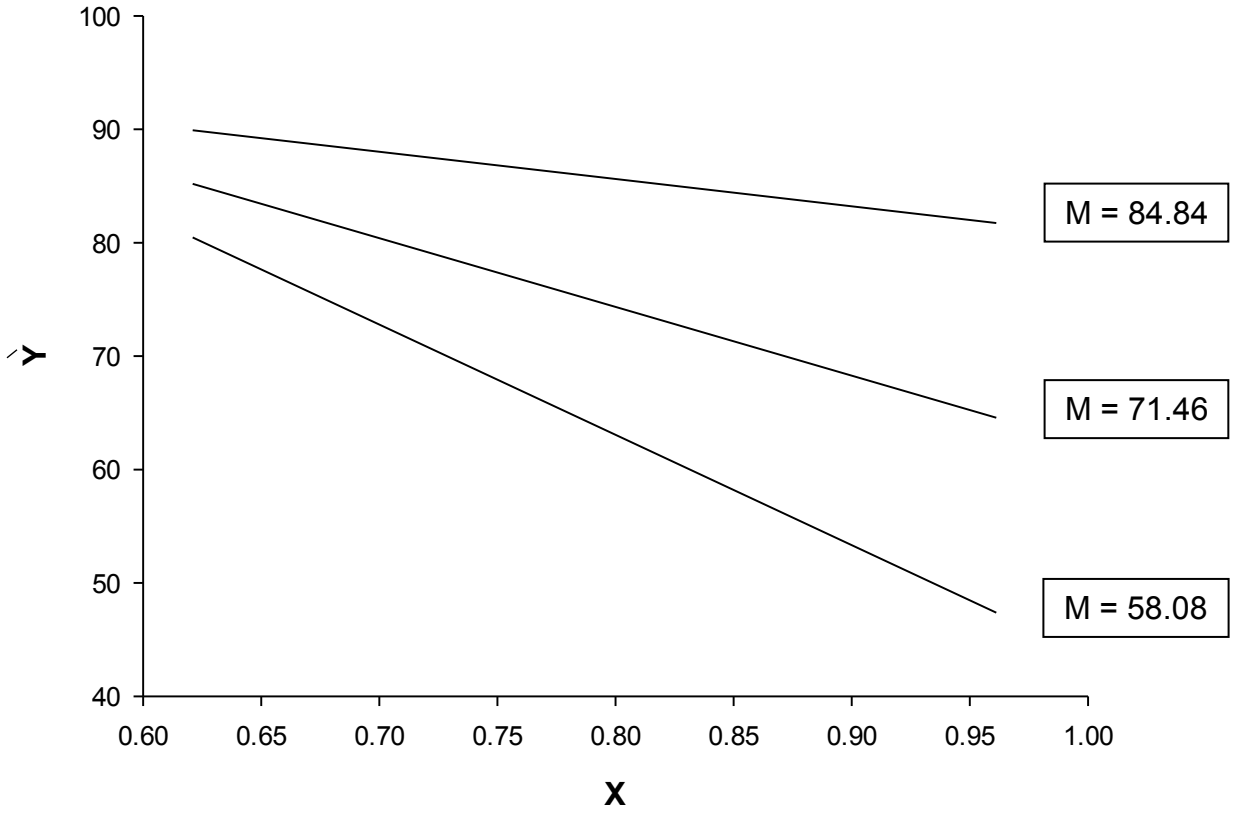
moderator in the relationship between $\dot{V}O_2$ and exercise adherence. Using the Johnson-Neyman technique, a cut-off value of 77.02 was identified, above which global vigor acted as a significant moderator. **Figure 18** illustrates predicted adherence ($\hat{Y}$) against $\dot{V}O_2$ for three levels of end-exercise global vigor.

Figure 17. Tested moderation model.



Conceptual moderation model (A) and statistical moderation model (B) with $\dot{V}O_2$ as the predictor (independent variable), global vigor at end-exercise as the moderator, and adherence as the outcome (dependent variable) while adjusting for attendance.

Figure 18. Predicted adherence against $\dot{V}O_2$ for three levels of end-exercise global vigor.



Predicted adherence against $\dot{V}O_2$ for three levels of end-exercise global vigor. Ŷ: predicted adherence; X: mean $\dot{V}O_2$; M: moderator.

5. DISCUSSION

In the present project, we compared the acute physiological, symptomatic, and affective responses to different exercise-training protocols in moderate-to-severe COPD patients with no significant resting or exercising oxygen desaturation and a relatively preserved exercise tolerance. Furthermore, we examined the relationship between measures of acute response to exercise training and subsequent adherence to a 12-week program. Our findings can be summarized as follows: i) affective state generally improved from rest to post-exercise; ii) CTVT was less physiologically demanding than CTHI and IT, was associated with a more pronounced drop in global affect midway through the training bout, but with less leg fatigue throughout and better vigor at the end of the bout; iii) IT was associated with a more pronounced ventilatory response than CTHI and CTVT, lower levels of alertness 30-minutes after the training bout and with a reduced 12-week adherence rate; iv) measures of acute exercise intensity, more specifically $\dot{V}O_2$, was most strongly and inversely related to 12-week adherence; and v) this relationship was moderated by global vigor at end-exercise.

Results from the present study on the acute physiological response to IT compared to CTHI differ from previous comparable reports, which showed a reduced metabolic strain with intermittent exercise compared to continuous high-intensity exercise [115, 117]. Inconsistencies between our results and those from Sabapathy and colleagues [115] are likely attributable to the disparity in the IT protocols used. The IT protocol used in our study consisted of shorter intervals (30 seconds versus 1 minute) of a higher relative intensity (100% versus 70% peak workload) alternated with active recovery (versus rest). These differences likely translated into less time for the cardio-

respiratory system to recuperate with our IT protocol, thereby making it more physiologically demanding. As for Vogiatzis et al. [117], our findings possibly differed from theirs due to disparities in the continuous training protocols. Their subjects were asked to maintain a wattage corresponding to 80% of peak workload [117]; in the present study, subjects were asked to remain within a ± 5 beats/min of the HR reached at 80% of peak workload on the incremental test, corresponding to approximately 60% of peak workload. Thus, our CTHI protocol was less physiologically demanding than theirs. It seems reasonable to conclude that depending on the protocols used, IT can be similarly, slightly more, or slightly less physiologically demanding than CTHI. Comparing CTHI and CTVT, despite differences in the specific exercise-training protocols utilized (50% HR reserve versus HR reached at 80% of peak workload), our results support Vallet et al.'s [116] findings suggesting that training at the ventilatory threshold is more tolerable physiologically for COPD patients than continuous training at a standardized intensity. However, the short-term and long-term effectiveness of CTVT in comparison to CTHI and IT remains to be determined. This question will be addressed by the larger clinical trial to which the present study was associated (OPTION).

The difference in leg fatigue experienced by the CTVT group compared to CTHI and IT disappeared when expressed as a percent peak. Additionally, CTVT was not associated with reduced dyspnoea ratings, as previously reported by Vallet et al. [116]. Ratings of perceived breathlessness have been suggested as unresponsive to increases in exercise performance [194] and declines in lung function over time in prior reports [195]. The presence of a dyspnoea threshold in COPD patients has also been proposed, a threshold that when surpassed may not be well tolerated [194]. Subjects may therefore

consciously or unconsciously select a level of dyspnoea not to surpass [194]. Our findings may reflect this phenomenon.

The overall improvement in affective state (increase in positive and/or global affect, and decrease in negative affect) observed from rest to post-exercise across training protocols is consistent with previous findings in healthy populations, which have shown acute exercise-induced increases in affect with various training intensities [196-199]. However, our results are not in line with the contention that affect improves or remains stable during exercise performed at the ventilatory threshold, and worsens when the intensity is above the ventilatory threshold. Indeed, the CTVT group, which exercised at 100% of its ventilatory threshold (Table 5), experienced the greatest dip in affect mid-exercise, while the CTHI and IT groups, which exercised above its ventilatory threshold (109% and 108%, respectively; Table 5), experienced less or no dip. One possible explanation for this finding is that COPD patients, who face discomfort on a regular basis, react differently than healthy individuals to different exercise intensities. As well, elevated rates of psychological and cognitive impairments have been documented in COPD patients [200-202]; these factors have been shown to impact affective response to exercise and may thus explain discrepancies between our findings and what has been shown in healthy individuals [203, 204]. Perhaps the CTVT group reached a state of boredom mid-exercise due to under arousal, as boredom has been previously linked with negative affect [203, 205]. Another possible explanation for the drop in global vigor as opposed to the expected maintenance or increase in the CTVT group is that intensities below or at the ventilatory threshold appear to be associated with greater

variability in the affective response to exercise compared to intensities above the ventilatory threshold [206, 207].

The present study suggests, for the first time in COPD patients, that vigor improves after a single exercise-training bout. Findings in healthy subjects have also shown improvements in vigor from pre- to post-exercise irrespective of exercise intensity [208, 209]. In a crossover study conducted by Steptoe et al. [210], a sample consisting of 32 healthy subjects were asked to cycle twice at a low intensity (25 Watts) and twice at a high-intensity (100 Watts), at random, during a single visit. Results revealed an increase in end-exercise vigor in the low-intensity group and a decrease in end-exercise vigor in the high-intensity group, however, only the former was significant [210]. Our findings are in line with this study since the lowest intensity protocol, CTVT, was associated with higher levels of alertness at end-exercise while the highest intensity protocol, IT, was associated with lower levels of alertness 30 minutes post-exercise.

Our results on adherence to the different exercise-training protocols revealed a significantly lower percentage of time spent at the target intensity for IT (49%) compared to CTHI (86%) and CTVT (85%). To our knowledge, this is the first report on exercise adherence rates measured using continuous data tracking technology in COPD patients; nonetheless, this finding needs to be interpreted with caution because the present study was not designed nor powered to detect differences in adherence rates between the three training protocols. This study rather placed emphasis on the relationship between acute measures of exercise-training intensity and subsequent adherence to the training protocol to validate or invalidate conceptual models that had previously been proposed

for healthy populations. To that extent, our results suggest that acute measures of exercise intensity, more specifically $\dot{V}O_2$, is most strongly and negatively related to 12-week exercise adherence, possibly suggestive of an intensity-adherence trade-off as previously observed in healthy individuals [211, 212]. Although never empirically tested, the intensity-adherence trade-off is believed to be mediated by affect. In the present study, end-exercise global vigor was not found to mediate, but rather to moderate the relationship between $\dot{V}O_2$ (intensity) and 12-week adherence. More specifically, a cut-off value of 77 has been identified, above which, end-exercise global vigor seems to weaken the relationship between intensity and adherence, and under which end-exercise global vigor does not seem to act as a moderator. From a clinical perspective, measuring global vigor at the end of an exercise bout, especially during the beginning phases of a PR program, may provide valuable insight.

The present study needs to be interpreted in the context of some limitations. Firstly, our sample size was small when divided into the three subgroups, which may have affected our power. Post-hoc power calculations were thus performed on our main preliminary results, and power calculations ranging from 0.82 to 0.99 were obtained, suggesting sufficient power for those outcomes. Had a larger sample size been attained, several confounders would have been controlled for including smoking pack-years, fitness level, disease severity, etc. Secondly, although occurring by chance, our groups were composed of unequal samples. These baseline between-group differences were not statistically significant, yet were clinically meaningful. Furthermore, based on the general response to the incremental cycling test (Table 4), it is likely that the cardio-pulmonary response was submaximal for many patients, which poses an issue since

exercise prescription was derived from the values reached on these tests. Having a submaximal test translates into an under-estimated exercise prescription, where subjects may have trained below the targeted intensities. As well, the inability to place markers in the utilized data tracking software between the high and low intervals prevented us from precisely measuring adherence during the high intervals only. This may have caused a systematic over-estimation of our findings on exercise adherence to the prescribed intensity for the IT group. The adherence measurement was also slightly skewed and adherence rates were high overall, which did not provide a large spread of data (i.e. variance). Finally, a recruitment bias towards highly motivated individuals with perhaps higher adherence rates than normal may have occurred, which may limit the generalizability of our findings.

In summary, our results suggest that, compared to CTHI, CTVT is associated with reduced levels of RER, HR, and RR, while the IT protocol used in the present study is associated with higher levels of $\dot{V}_E$, $\dot{V}_E$ / MVV, and RR as well as an increased drop in SpO_2 from rest. From an affective viewpoint, affect generally appears to improve from rest- to post-exercise in COPD patients. Vigor, on the other hand, differs between protocols, where CTVT is associated with greater levels of alertness at end-exercise and IT is associated with lower levels of alertness post-exercise. Results on adherence to the 12-week training program suggest that IT is associated with significantly reduced adherence rates compared to CTHI and CTVT. However, this needs to be interpreted with caution as this study was not powered to assess adherence. Results on the relationship between intensity and adherence suggest that, $\dot{V}O_2$ is inversely related to 12-week adherence, possibly supportive of an intensity-adherence trade-off, and that

this relationship may be moderated by vigor. The present study suggests CTVT as an appealing exercise protocol, yet the short- and long-term effectiveness of this approach needs to be validated against CTHI and IT before any recommendations can be made.

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7. APPENDIX A: Manuscript - Using Continuous Data Tracking Technology to Study Exercise Adherence in Pulmonary Rehabilitation (Published)

Link to video: http://www.jove.com/video/50643/using-continuous-data-tracking-technology-to-study-exercise-adherence

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Keywords: Data tracking, exercise, rehabilitation, adherence, patient compliance, health behavior, user-computer interface.

Short Abstract:

Pulmonary rehabilitation is widely recognized in the management of respiratory diseases. A key component to successful pulmonary rehabilitation is adherence to the recommended exercise training. The purpose of the present protocol is to describe how continuous data tracking technology can be used to precisely measure adherence to a prescribed aerobic training intensity.

Long Abstract:

Pulmonary rehabilitation (PR) is an important component in the management of respiratory diseases. The effectiveness of PR is dependent upon adherence to exercise training recommendations. The study of exercise adherence is thus a key step towards the optimization of PR programs. To date, mostly indirect measures, such as rates of participation, completion and attendance, have been used to determine adherence to PR. The purpose of the present protocol is to describe how continuous data tracking technology can be used to measure adherence to a prescribed aerobic training intensity on a second-by-second basis.

In our investigations, adherence has been defined as the percent time spent within a specified target heart rate range. As such, using a combination of hardware and software, heart rate is measured, tracked, and recorded during cycling second-by-second for each participant, for each exercise session. Using statistical software, the data is subsequently extracted and analyzed. The same protocol can be applied to determine adherence to other measures of exercise intensity, such as time spent at a specified wattage, level, or speed on the cycle ergometer. Furthermore, the hardware

and software is also available to measure adherence to other modes of training, such as the treadmill, elliptical, stepper and arm ergometer. The present protocol, therefore, has a vast applicability to directly measure adherence to aerobic exercise.

INTRODUCTION:

Pulmonary rehabilitation (PR) combines exercise training, patient education and psychosocial support, and is widely recognized as a cornerstone in the management of pulmonary disease[1-5]. The goals of PR are to reduce symptoms, optimize functional status, improve health-related quality of life, and reduce health care costs[4,5]. In a meta-analysis of 31 randomized controlled trials in chronic obstructive pulmonary disease (COPD), PR was shown to significantly improve exercise capacity, reduce dyspnea and fatigue, improve emotional function and enhance patients' sense of control over their condition[6]. Furthermore, evidence documents its effectiveness in reducing respiratory exacerbations[7] and days spent in hospital[8-13]. Exercise training is considered the key to successful PR since it is responsible for much of the benefits associated with this intervention[3-5]. However, a major issue for several patients is adhering to the recommended amount or level of exercise. Non-adherence to recommended treatment may result in the failure of therapeutic interventions as well as inefficient use of health resources[14].

According to the World Health Organization, the term "adherence" refers to the extent to which a person's behavior coincides with recommendations given by a health care professional[15]. To date, adherence to exercise training in rehabilitation settings has been largely assessed as either the rate of participation (i.e., registration to the

program), the rate of completion (i.e., finishing the program), or the rate of attendance (i.e., number of exercise sessions attended)[16-18]. At present, no "gold standard" exists for measuring adherence[15] and current methods do not allow for great precision. Furthermore, depending on the selected method, rates of adherence to PR have shown large variability[16-19]. For example, Hogg et al.[16] measured adherence in COPD patients as the ratio between those who completed the program to those referred and found a low adherence of approximately 40%. However, other PR studies that have used attendance rates demonstrated, on average, a 90% adherence[10,20,21]. The lack of homogeneity in calculating adherence makes it difficult to compare results between studies. Another concern is the lack of precision with the existing calculation methods; attendance to an exercise training session does not guarantee adherence to the prescribed intensity. This gap in information led us to investigate how adherence could be calculated in a more precise way.

Recent advances in fitness equipment technology have allowed for continuous data tracking, which can be used to monitor adherence to a prescribed aerobic training intensity during individual exercise sessions in a PR context. More specifically, data tracking hardware and software permits for second-by-second recording of duration, speed, level, wattage, pace, heart rate, distance, calorie consumption, $\dot{V}O_2$, METS, and calories, and provides averages of all variables with the exception of level and $\dot{V}O_2$. The main advantage of this technology is the ability to record continuous detailed measures, which allows for the precise calculation of adherence to prescribed exercise versus previously reported general attendance or completion rates. This procedure can be of value for any study examining the impact of one or several aerobic exercise

training programs. Using this technology, patient adherence to a prescribed intensity can be assessed by the percent time spent at a specified wattage, level, speed, or heart rate during the training phase of each session. For our investigations, adherence to an exercise training protocol has been defined as the percent time spent within a specified target heart rate range. Since heart rate response at a given submaximal workload decreases as cardiorespiratory fitness increases, this approach ensures that patients remain at the same relative (versus absolute) training intensity throughout the program. The present protocol describes in detail how continuous data tracking technology can be used to precisely measure adherence to a prescribed target heart rate range.

PROTOCOL:

Once data is collected, a single file per subject per session of raw data is obtained. Using statistical software, all sessions per subject are combined into a single file. Subsequently, the target intensity must be calculated for each subject. The adherence rate to that target intensity can then be calculated per session per subject, for each session for all subjects combined, or per group.

1. Data collection (carried out by personnel supervising the training session)

1.1 Minimize electrical interference by turning off wireless devices (e.g. cell phones, Wi-Fi, etc.) and minimize crosstalk by ensuring the heart rate monitors and equipment are at least 1 meter apart. Refer to Figure 1 for placement of heart rate transmitter.

1.2 Turn on the data tracking software. Press start on the aerobic equipment and train the participant at the target intensity. For example, in our studies, participants are

asked to train within ± 5 beats/min of their target heart rate. Refer to Figure 2 for CardioMemory.

1.3 Collect data second-by-second for each participant for each rehabilitation session. Collected data includes the following: subject ID, duration (hhmmss), level of intensity (1-30), workload (watts), pedalling speed (revolutions/minute), distance (km), pace (mm:ss/km), heart rate (beats/minute), estimated oxygen consumption ($\dot{V}O_2$, ml/min/kg), metabolic equivalent of physical effort (METs), estimated energy expenditure (kcal/hour), and estimated energy consumed (kcal). See Figure 3.

1.4 Press stop on the aerobic equipment. Click “save” to upload the data to CardioMemory. Click “export” to save the document outside of CardioMemory. The document will be in .cvs format and will automatically include the date of the session.

2. Data extraction

CardioMemory software does not allow for the distinction of various exercise-training phases. As such, the data obtained must be exported to a statistical software in order to eliminate the phases that are not of interest (e.g. warm-up and cool-down), merge the data files, and compare achieved against target intensity.

2.1 Open statistical analysis software to import excel file. Procedure: *File* → *Open* → *Data* → In “Open Data” window, select *All Files* in the dropdown menu of “Files of Types” → Select Excel. xls file → *Open* → In “Opening Excel Data Source” window click *OK*.

2.2 Save the data file in a statistical analysis software. See Figure 4 for a sample database.

2.3 Eliminate the non-training phases, i.e., warm-up and cool-down, if the interest is time spent at the target intensity during the training phase.

2.3.1 Eliminate warm-up phase (e.g. first 10 minutes):

2.3.1.1 To recode duration, create a variable to identify every second as 1. Procedure: *Transform* → *Recode into Different variables…* → In "Recode into Different Variables" window, select *Duration_A* → click arrow → Identify "Output Variable Name" (e.g. *tempo*) → *Change* → Click on *Old and New Values* → Under “Old Value”, select *Value:* and enter 0 → Under “New Value”, Select *Value:* and enter 0 → *Add* → Under “Old Value”, select *All other values* then click on *Value:,* under "New Value" and enter 1 → *Add* → *Continue* → *OK*.

```
RECODE Duration_A (0=0) (ELSE=1) INTO Tempo.
EXECUTE.
```

2.3.1.2 Create a second temporary variable. Procedure: *Transform* → *Shift Values* → Select tempo → Click arrow → Under "Name:" type temporary variable (e.g. *tempo2*) → *Change* → *OK*.

```
SHIFT VALUES VARIABLE=Tempo RESULT=Tempo2 LAG=1.
```

2.3.1.3 To start *tempo2* at 0, it must be recoded. Procedure: *Transform* → *Recode into Same Variables* → Select *tempo2* → Click arrow → Click *Old and New Values* → Under "Old Value", select *System-Missing* → Under "New Value", select *Value:* and enter 0 → *Add* → *Continue* → *OK*.

```
RECODE Tempo2 (SYSMIS=0).
EXECUTE.
```

2.3.1.4 Sum the seconds starting from zero. Procedure: *Transform* → *Compute Variable* → Under "Target Variable:" type tempo → Under "Numeric Expression" type lag (tempo) +1 → IF... → Select *Include if case satisfies condition:* → Type tempo2 > 0 → *Continue* → *OK.*

```
IF  (Tempo2 > 0) Tempo=Lag (tempo) + 1.
EXECUTE.
```

2.3.1.5 To eliminate the first 10 minutes of warm-up, remove tempo data that precedes 599 seconds. Procedure: *Data* → *Select cases…* → In "Select Cases" window, under

"Select", choose "If condition is satisfied" → *If…* → In "Select Cases: If" window, insert equation tempo > 599 → *Continue* → Under "Output", choose *Delete unselected cases* → *OK*. See Figure 5.

```
FILTER OFF.
USE ALL.
SELECT IF (tempo > 599).
EXECUTE.
```

2.3.2 Eliminate cool-down phase (e.g. last 5 minutes):

2.3.2.1 Sort data in descending order for *Duration_A* to bring the cool-down phase to the top of the database, as SPSS removes data from the top of the file onwards. Procedure: *Data* → *Sort Cases* → In "Sort Cases" window, select *Duration_A* → click arrow → In "Sort Order" menu select *Descending* → *OK*.

```
SORT CASES BY Duration_A(D).
```

2.3.2.2 Recode *Duration_A* to identify every second as 1. Procedure: *Transform* → *Recode Into Different variables…* → In "Recode into Different Variables" window, select *Duration_A* → click arrow → Identify "Output Variable Name" (e.g. *tempoA*) → Change → Click *Old and New Values* → Under "Old Value", select *Value:* and enter 0 → Under "New Value", select *Value:* and enter 0 → *Add* → Select *All other values* under "Old Value", then click on *Value:* under "New Value" and enter 1 → *Add* → *Continue* → *OK*.

RECODE Duration_A (0=0) (ELSE=1) INTO TempoA.

EXECUTE.

2.3.2.3 Create a second temporary variable. Procedure: *Transform* → *Shift Values* → Select tempoA → Click arrow → Under "Name:" type temporary variable (e.g. *tempoA2*) → *Change* → *OK*.

SHIFT VALUES VARIABLE=TempoA RESULT=TempoA2 LAG=1.

2.3.2.4 To start tempoA2 at 0, it must be recoded. Procedure: *Transform* → *Recode into Same Variables* → Select *tempoA2* → Click arrow → Click *Old and New Values* → Under "Old Value", select *System-Missing* → Under "New Value", select *Value:* and enter 0 → *Add* → *Continue* → *OK*.

RECODE TempoA2 (SYSMIS=0).

EXECUTE.

2.3.2.5 Sum the seconds of the tempoA variable. Procedure: *Transform* → *Compute Variable* → Under "Target Variable:" type tempoA → Under "Numeric Expression" type lag (tempoA)+1 → IF... → Select *Include if case satisfies* condition: → Type tempoA2> 0 →*Continue* → *OK.*

IF (TempoA2 > 0) TempoA=Lag (tempoA) + 1.

EXECUTE.

2.3.2.6 To eliminate the cool-down phase (i.e. 5 minutes), remove tempo data that precedes 299 seconds. Procedure: *Data* → *Select cases…* → In "Select Cases" window, under "Select", choose "If condition is satisfied" → *If…* → In "Select Cases: If" window, insert equation tempoA > 299 → *Continue* → under "Output", choose *Delete unselected cases* → *OK*. See Figure 6.

FILTER OFF.
USE ALL.
SELECT IF (tempoA > 299).
EXECUTE.

2.4 Identify the session number (or date) associated with the dataset. Create and name a new variable (e.g. *Session*). Procedure: *Transform* → *Compute Variable* → In compute variable window under *Target Variable*, type Session → click *Type & Label* to open "Compute Variable: Type an..." window → under "Type" select *String* → *Continue* → under *String Expression* type '1' → *OK*. See Figure 7.

STRING Session (A8).
COMPUTE Session= '1'.
EXECUTE.

2.5 Save the modified SPSS document in a new file (example: subjectID_session#).

2.6 Repeat the above procedure for all remaining sessions for the same subject.

3. Data merging - single participant

3.1 To merge all sessions into a single SPSS database, open participant's first session (i.e. subjectID_session1).

3.2 Merge remaining sessions to the current file. Procedure: *Data* → *Merge Files* → *Add Cases* → in "Add Cases to *subjectID_session1.sav*" window, click *Browse* and choose file *subjectID_session2* → *Open* → *Continue* → in the "Add Cases from ..." window click *OK.* Repeat for all remaining sessions. See Figure 8.

```
ADD FILES /FILE=*
/FILE='SubjectAB001_Session1.sav'.
EXECUTE.
```

3.3 Add a column which contains the subject's ID number. Procedure: *Transform* → *Compute Variable* → In “Compute Variable” window under *Target Variable*, type SubjectID → click *Type & Label* to open "Compute Variable: Type an..." window → under "Type" select *String* → *Continue* → under *String Expression* type 'SubjectID' (e.g.*'AB001'*) → *OK*. See Figure 9.

```
STRING  Subject_ID (A8).
```

COMPUTE Subject_ID='AB001'.

EXECUTE.

3.4 Add a column that contains the subject's target intensity (e.g. target heart rate [THR]). Procedure: *Transform* → *Compute Variable* → In "Compute Variable" window under *Target Variable*, type THR → click *Type & Label* to open "Compute Variable: Type an..." window → under "Type" select *Numeric* → *Continue* → under *Numeric Expression* type THR (e.g. *110*) → *OK*. See Figure 10.

STRING THR (A8).

COMPUTE THR='110'.

EXECUTE.

3.5 Save database under a different file name (e.g. *SubjectAB001_session1-36*).

3.6 Repeat for all remaining participants. At this point, each participant will have a database containing all sessions.

4. Data merging - grouping participants

4.1 To group several participants into a single database, open participant's file (i.e. subjectID_session1-36).

4.2 Merge the remaining participants to the current file. Procedure: *Data* → *Merge Files* → *Add Cases* → in "Add Cases to *SubjectAB001_session1-36.sav*" window, click *Browse* and choose file *SubjectCD002_session1-36* → *Open* → *Continue* → in the "Add Cases from ..." window click *OK.* Repeat for all participants that you wish to group. See Figure 11.

```
ADD FILES /FILE=*
/RENAME (AB001=d0)
/FILE='SubjectAB001_Session1-36.sav'
  /RENAME (CD002=d1)
/DROP=d0 d1.
EXECUTE.
```

4.3 Save new database (e.g. *Group01_Subjects001-010*).

5. Identification of Target Intensity (e.g. THR Range)

5.1 Identify a THR range; click *Transform* → *Compute Variable* → in the “Compute Variable” window under "Target Variable" enter a new variable name (e.g. Diff_HR_THR) → “Type & Label...” → in the “Compute Variable: Type an....” select *Numeric* → *Continue* → Under "Numeric Expression" enter equation: HR - THR → *OK.* This provides us with a new variable.

```
COMPUTE Diff_HR_THR=HR - THR.
```

EXECUTE.

5.2 Recode variables to identify whether the HR lies below, above, or within the THR range.

Procedure: *Transform* → *Recode Into Different Variables...* → select *Diff_HR_THR* → click arrow → under "Output Variable" under "Name" type Diff_HR_THR _recoded → *Change* → *Old and New Values...*→ in "Recode Into Different Variables: Old and New Values" window:

Old Value	**New Value**		**Old-->New:**
Range: *-5* through *5*	1	Add	-5 thru 5 --> 1
Range, LOWEST through value: *-5*	0		Lowest thru -5 --> 0
Range, value through HIGHEST: *5*	0		5 thru Highest --> 0
System-missing	System-missing		SYSMIS --> SYSMIS

→ *Continue* → *OK*. See Figure 12.

RECODE Diff_HR_THR (SYSMIS=SYSMIS) (-5 thru 5=1) (Lowest thru -5=0) (5 thru Highest=0) INTO

Diff_HR_THR_Recoded.

EXECUTE.

6. Calculation of Percent Adherence

6.1 In *Group01_Subjects001-010* file*,* calculate all seconds that patients were within the THR range by doing the following: *Data* → *Aggregate* → in "Aggregate Data"

window, under "Break Variable(s):" select *subjectID* and *session* → click arrow → under "Summaries of Variable(s):" select *Diff_HR_THR _recoded* → click arrow → *OK*. A new variable is created with the name *Diff_HR_THR _recoded_mean.*

```
AGGREGATE
  /OUTFILE=* MODE=ADDVARIABLES
  /BREAK=Subject_ID Session
  /Diff_HR_THR_Recoded_mean=MEAN(Diff_HR_THR_Recoded).
```

6.2 Convert the obtained value into a percentage; click *Transform* → *Compute Variable* → under "Target Variable" enter variable name (e.g. Perc_THR) → under "Numeric Expression" select *Diff_HR_THR _recoded_mean* → click arrow → multiply the value by 100 (*Diff_HR_THR _recoded_mean * 100)* → *OK.* We then obtain adherence as a percentage of time spent within the THR for each subject for each session. See Figure 13

```
COMPUTE Perc_THR=Diff_HR_THR_Recoded_mean * 100.
EXECUTE.
```

6.3 To obtain adherence for the percentage of time spent within the THR for each subject for all sessions combined, in "Aggregate Data" window, under "Break Variable(s):" substitute *subjectID* and *session* with only *subjectID*. See Figure 14.

6.4 To obtain adherence for the percentage of time spent within the THR for each session for all subjects combined, in "Aggregate Data" window, under "Break Variable(s):" substitute *subjectID* and *session* with only *session*.

6.5 Save the database under a different file name (e.g. *Group01_Subjects001-010_Aggregate*).

REPRESENTATIVE RESULTS:

When the protocol is performed correctly, an adherence rate is obtained for each subject for each session (Figure 13), for each subject for all sessions (Figure 14), and for each session for all subjects combined. An estimate of the time required to complete the above protocol for a single session of one subject is approximately 5 minutes. Results for adherence can range from 0% to 100%. Using this information, additional analyses can be performed to determine differences between subjects (i.e. sex differences, disease severity, etc.), to identify changes over time, and to reveal patterns in adherence. Moreover, the comparison of adherence between groups can be performed; for example, different exercise-training programs can be compared. Finally, through further investigation, causes of non-adherence can be identified at specific time points during PR.

FIGURES:

Figure 1: Heart rate transmitter placement.

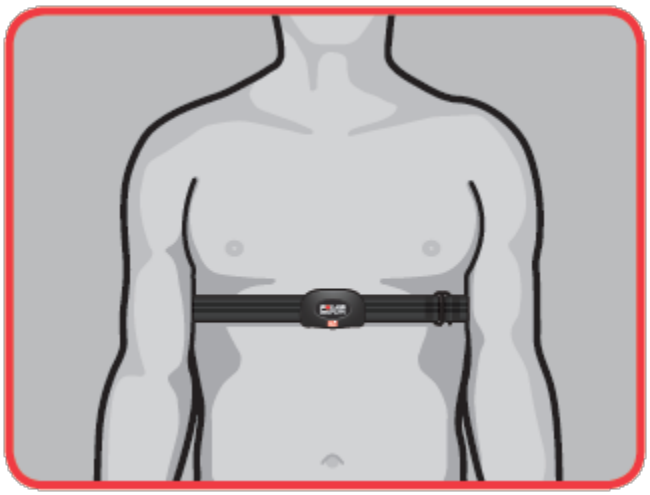


Figure 2: Sample of data collected using data tracking software.

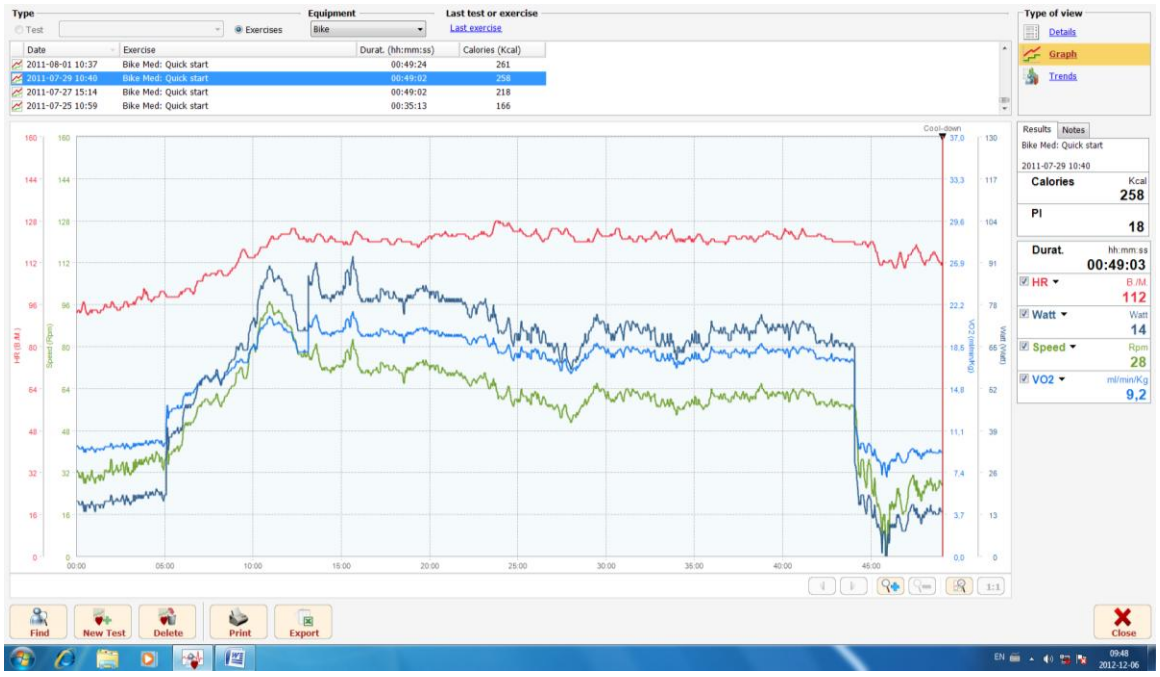


Figure 3: Sample of data tracking software output.

Club Member	AB123	Durat. (hh:mm:ss)	00:21:01
Age (years)	64	Durat. (sec.)	1261
Weight (Kg)	64	Calories (Kcal)	96
Exercise	Bike Med: Quick start	Distance (Km)	6,65
Equipment	BIKE MED	Average HR (B./M.)	91
Date/time	2009-05-06 11:36	P.I.	22
Doctor/Trainer	ADMINISTRATOR Administrator	Avg. Watts (Watt)	46
		Average speed (Rpm)	59
		Mets	3,9
		Pace (mm:ss/km)	00:03:10

Durat. (hh:mm:ss)	Speed (Rpm)	Calorie cons. (Kcal/h)	%HR (%HR)	Level	Watt (Watt)	Pace (mm:ss/km)	HR (B./M.)	VO2 (ml/min/Kg)	Mets (Mets)	Calories (Kcal)	Distance (Km)
00:00:01	37	200	32	1	19	00:00:00	61	10	2,9	0	0
00:00:02	37	200	32	1	19	00:00:00	61	10	2,9	0	0
00:00:03	38	200	32	1	20	00:04:52	61	10,2	2,9	0	0,01
00:00:04	38	200	32	1	20	00:04:52	61	10,2	2,9	0	0,01
00:00:05	39	202	32	1	20	00:04:44	61	10,2	2,9	0	0,01
00:00:06	39	204	32	1	20	00:04:44	60	10,2	2,9	0	0,01
00:00:07	40	202	32	1	21	00:04:37	60	10,3	2,9	0	0,02
00:00:08	40	204	31	1	21	00:04:37	59	10,3	2,9	0	0,02
00:00:09	41	206	31	1	21	00:04:31	59	10,3	2,9	0	0,02
00:00:10	41	206	31	1	21	00:04:31	59	10,3	2,9	0	0,03
00:00:11	41	206	31	1	21	00:04:31	59	10,3	2,9	0	0,03
00:00:12	42	206	31	1	21	00:04:24	59	10,3	2,9	0	0,03
00:00:13	42	206	31	1	21	00:04:24	58	10,3	2,9	0	0,04
00:00:14	43	206	31	1	22	00:04:18	58	10,5	3	0	0,04
00:00:15	44	206	31	1	22	00:04:12	58	10,5	3	0	0,05

Figure 4: Sample database illustrating a sample of statistical software database.

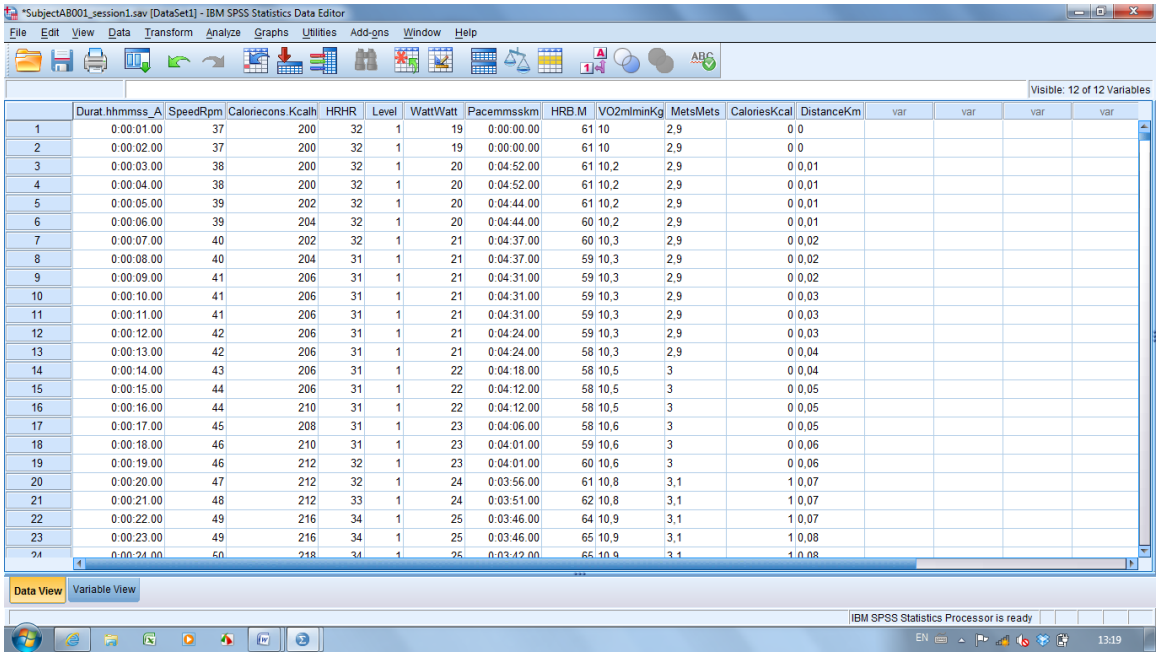


Figure 5: Sample database illustrating the eliminated warm-up phase.

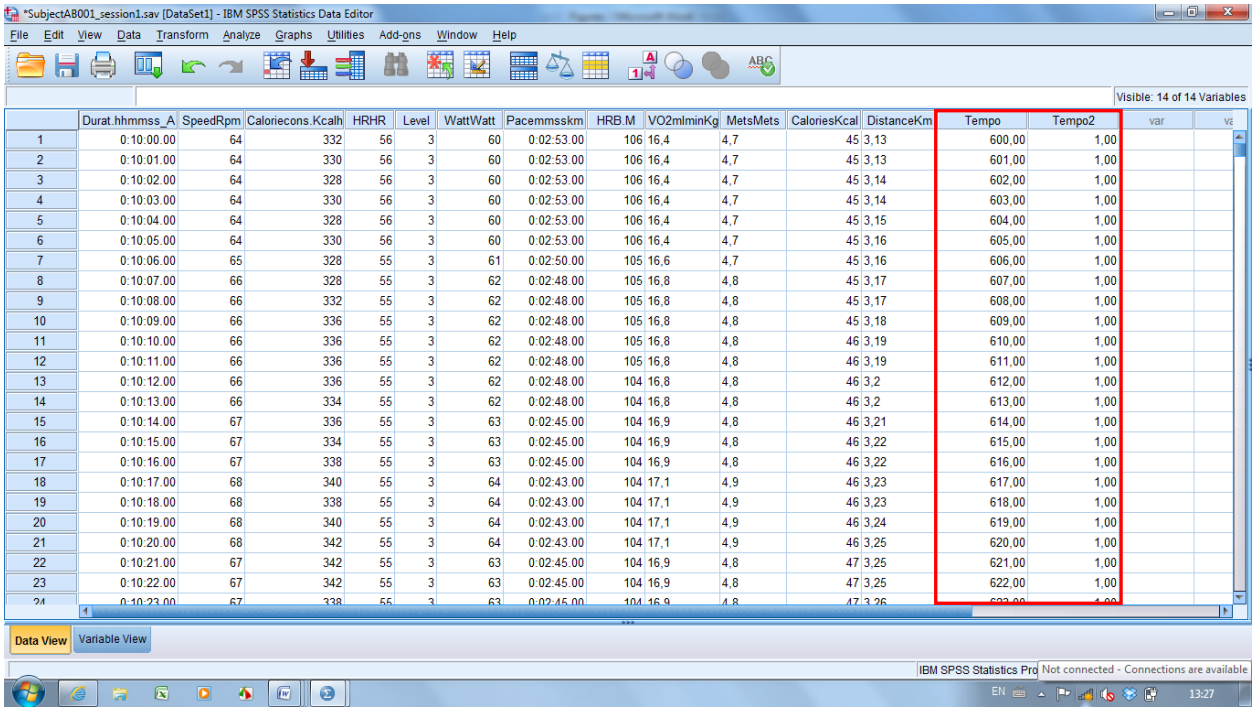


Figure 6: Sample database illustrating the eliminated cool-down phase.

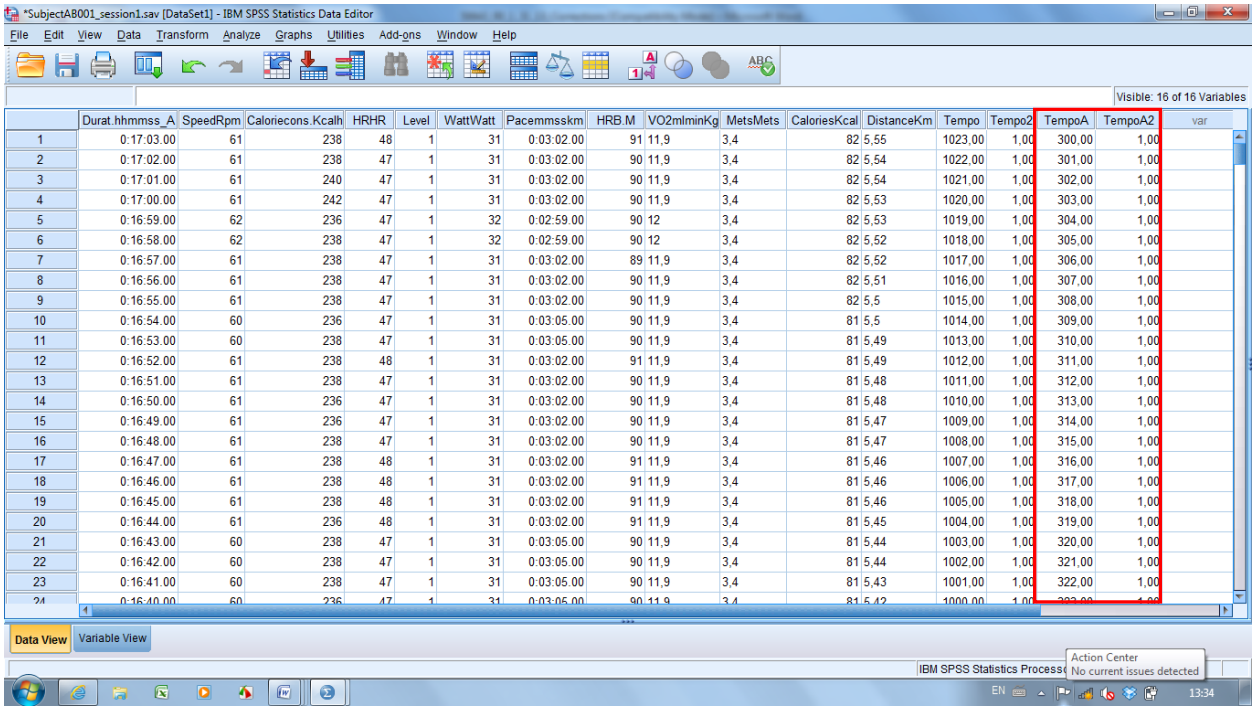


Figure 7: Sample database illustrating a column added for session number.

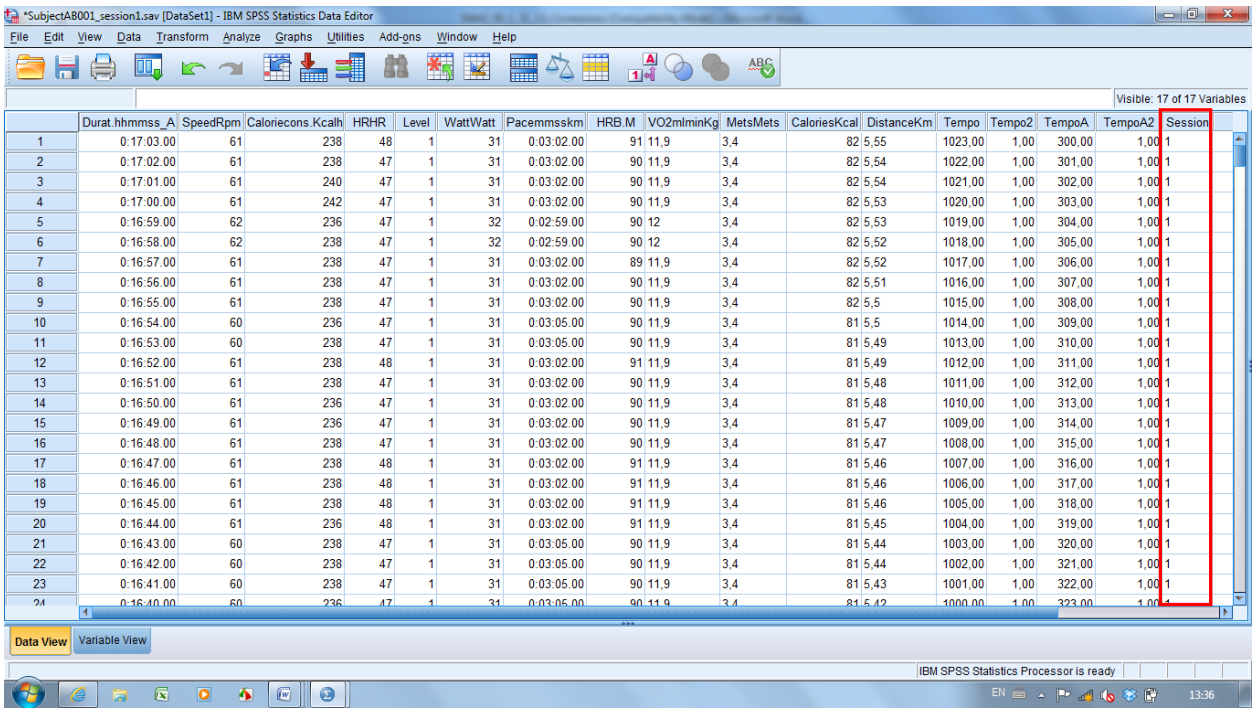


Figure 8: Sample database illustrating the merged sessions for a single participant.

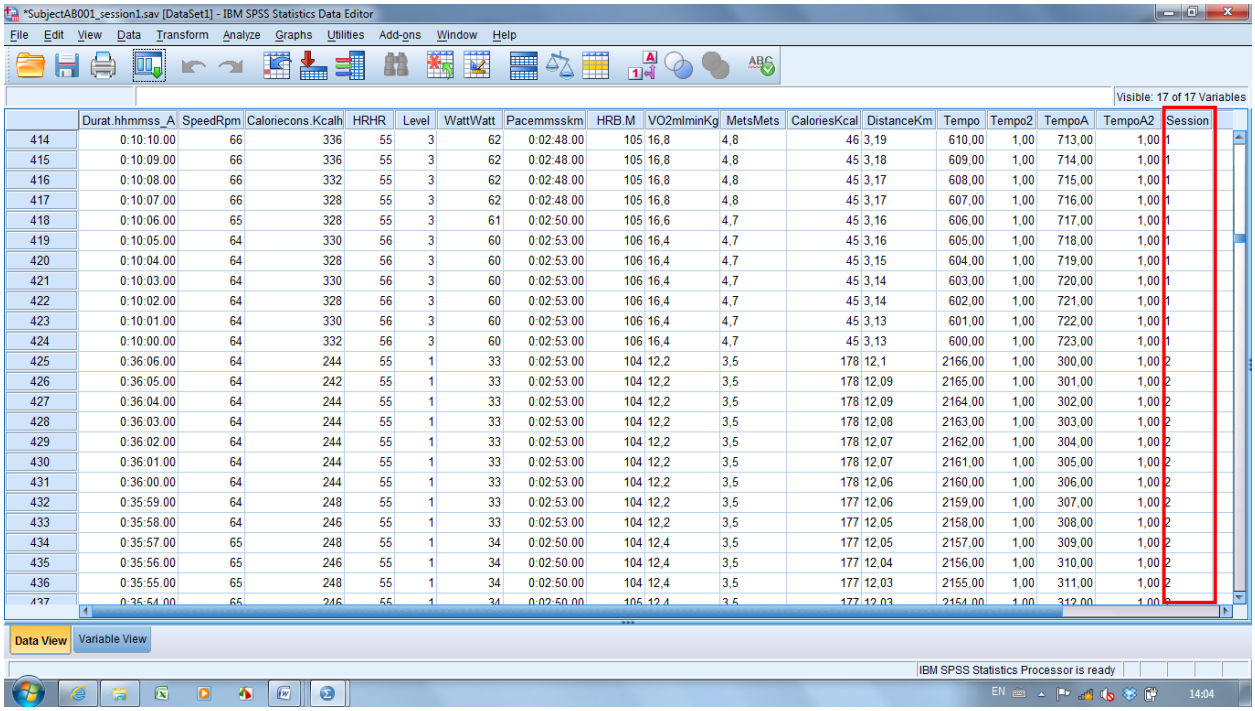


Figure 9: Sample database illustrating a column added for subject identification number.

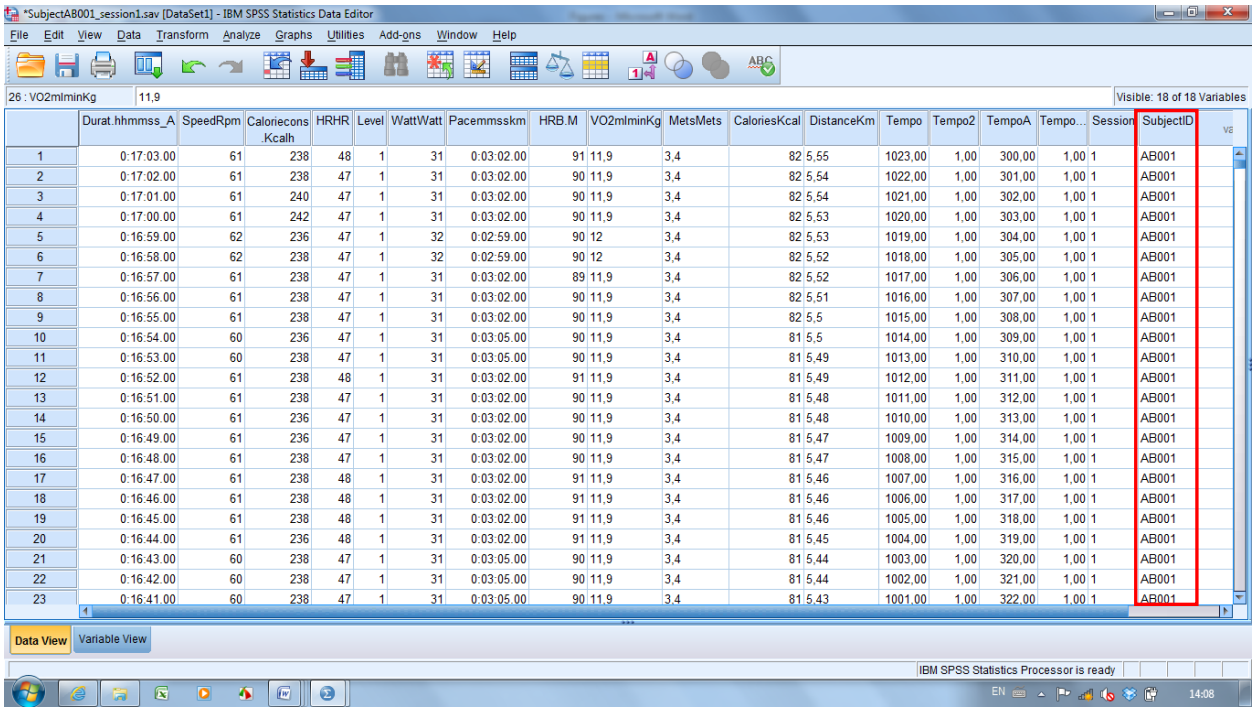


Figure 10: Sample database illustrating a column added for target heart rate.

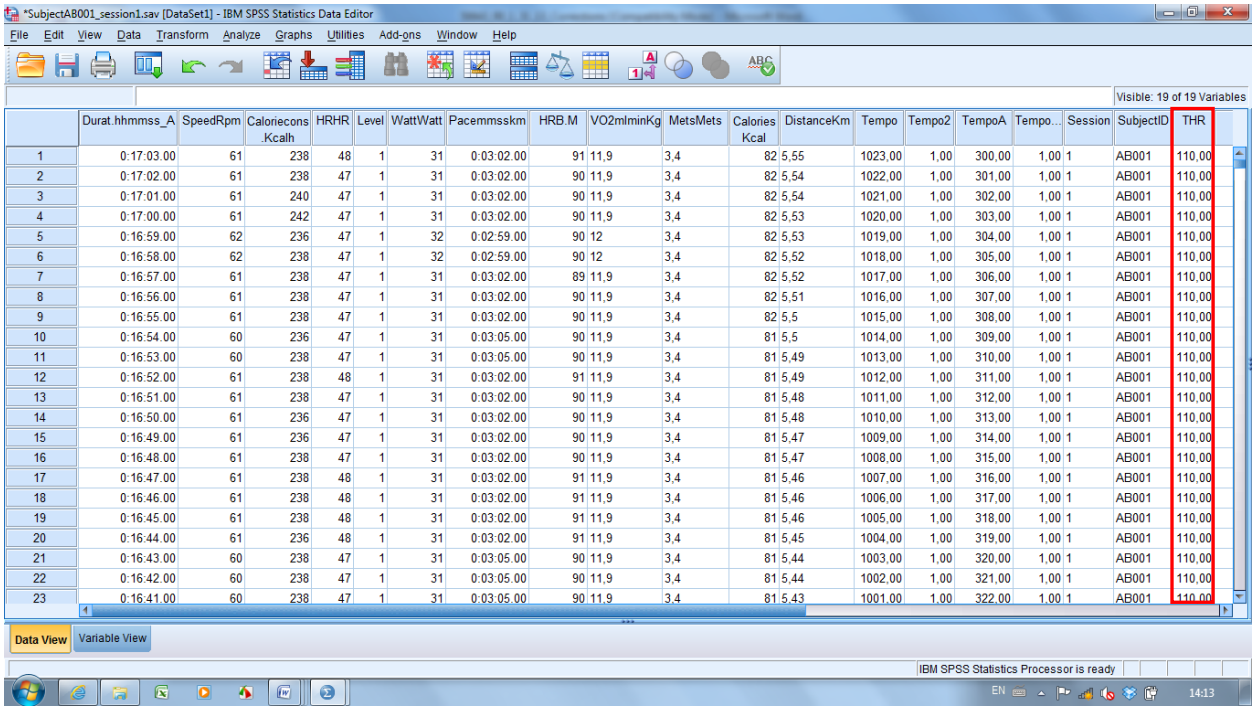


Figure 11: Sample database illustrating the merged participants' files.

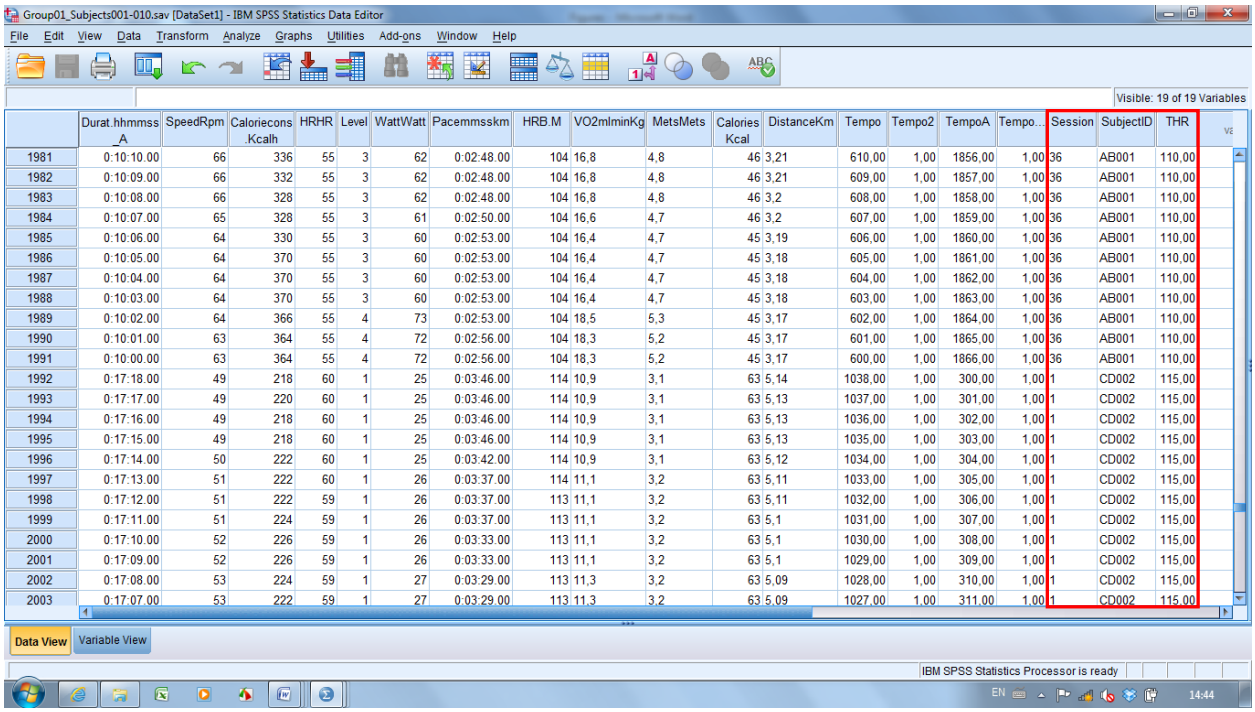
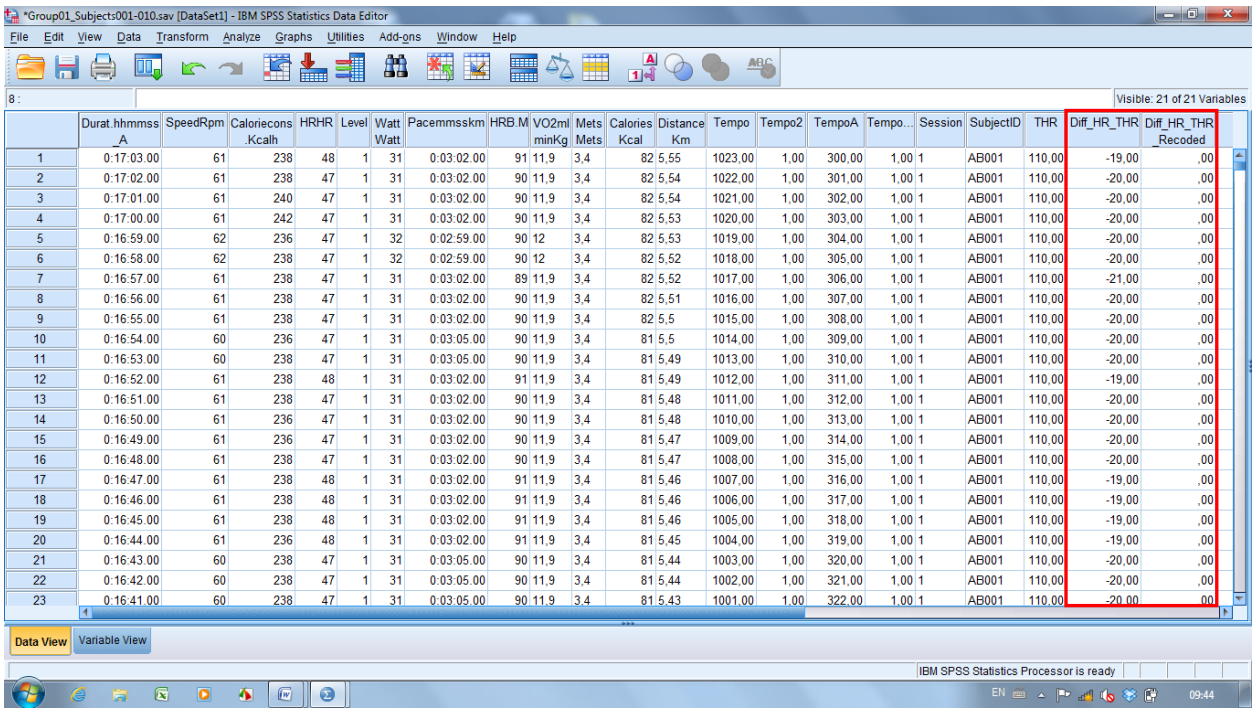
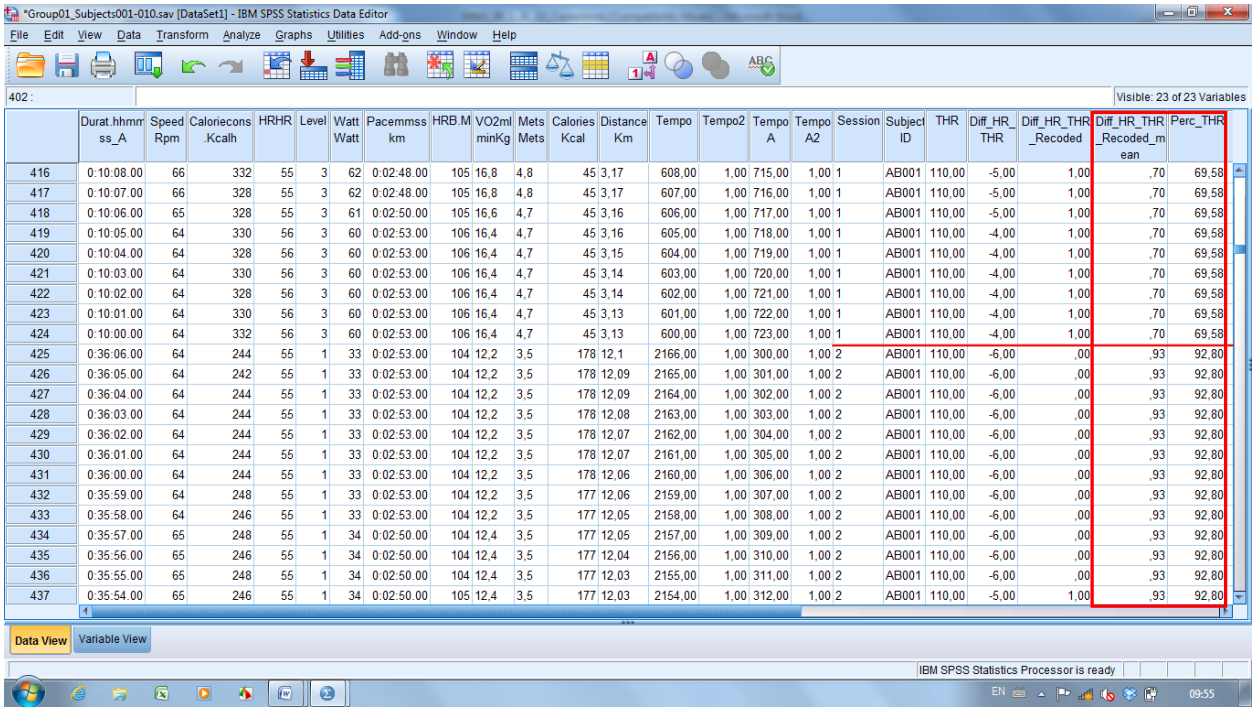


Figure 12: Sample database illustrating the recoded heart rate variables.



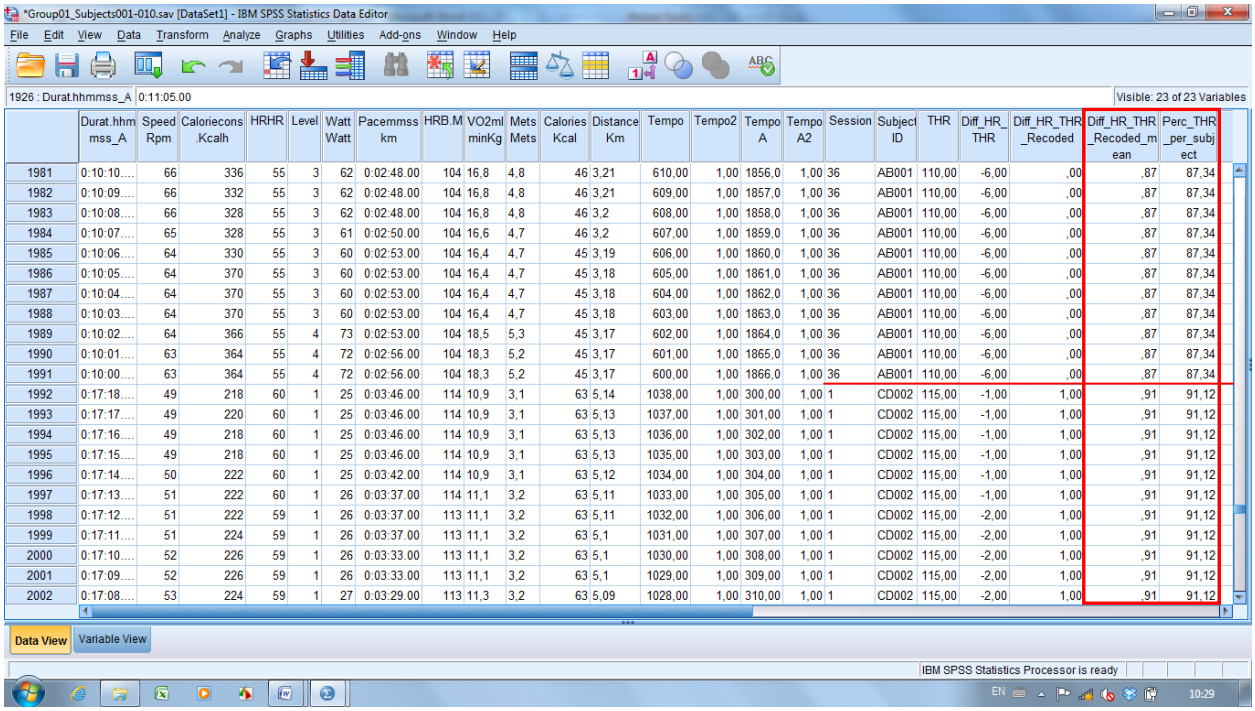
	Durat.hhmmss_A	SpeedRpm	Caloriecons.Kcalh	HRHR	Level	Watt Watt	Pacemmsskm	HRB.M	VO2ml minKg	Mets Mets	Calories Kcal	Distance Km	Tempo	Tempo2	TempoA	Tempo...	Session	SubjectID	THR	Diff_HR_THR	Diff_HR_THR_Recoded
1	0:17:03.00	61	238	48	1	31	0:03:02.00	91	11,9	3,4	82	5,55	1023,00	1,00	300,00	1,00	1	AB001	110,00	-19,00	,00
2	0:17:02.00	61	238	47	1	31	0:03:02.00	90	11,9	3,4	82	5,54	1022,00	1,00	301,00	1,00	1	AB001	110,00	-20,00	,00
3	0:17:01.00	61	240	47	1	31	0:03:02.00	90	11,9	3,4	82	5,54	1021,00	1,00	302,00	1,00	1	AB001	110,00	-20,00	,00
4	0:17:00.00	61	242	47	1	31	0:03:02.00	90	11,9	3,4	82	5,53	1020,00	1,00	303,00	1,00	1	AB001	110,00	-20,00	,00
5	0:16:59.00	62	236	47	1	32	0:02:59.00	90	12	3,4	82	5,53	1019,00	1,00	304,00	1,00	1	AB001	110,00	-20,00	,00
6	0:16:58.00	62	238	47	1	32	0:02:59.00	90	12	3,4	82	5,52	1018,00	1,00	305,00	1,00	1	AB001	110,00	-20,00	,00
7	0:16:57.00	61	238	47	1	31	0:03:02.00	89	11,9	3,4	82	5,52	1017,00	1,00	306,00	1,00	1	AB001	110,00	-21,00	,00
8	0:16:56.00	61	238	47	1	31	0:03:02.00	90	11,9	3,4	82	5,51	1016,00	1,00	307,00	1,00	1	AB001	110,00	-20,00	,00
9	0:16:55.00	61	238	47	1	31	0:03:02.00	90	11,9	3,4	82	5,5	1015,00	1,00	308,00	1,00	1	AB001	110,00	-20,00	,00
10	0:16:54.00	60	236	47	1	31	0:03:05.00	90	11,9	3,4	81	5,5	1014,00	1,00	309,00	1,00	1	AB001	110,00	-20,00	,00
11	0:16:53.00	60	238	47	1	31	0:03:05.00	90	11,9	3,4	81	5,49	1013,00	1,00	310,00	1,00	1	AB001	110,00	-20,00	,00
12	0:16:52.00	61	238	48	1	31	0:03:02.00	91	11,9	3,4	81	5,49	1012,00	1,00	311,00	1,00	1	AB001	110,00	-19,00	,00
13	0:16:51.00	61	238	47	1	31	0:03:02.00	90	11,9	3,4	81	5,48	1011,00	1,00	312,00	1,00	1	AB001	110,00	-20,00	,00
14	0:16:50.00	61	236	47	1	31	0:03:02.00	90	11,9	3,4	81	5,48	1010,00	1,00	313,00	1,00	1	AB001	110,00	-20,00	,00
15	0:16:49.00	61	236	47	1	31	0:03:02.00	90	11,9	3,4	81	5,47	1009,00	1,00	314,00	1,00	1	AB001	110,00	-20,00	,00
16	0:16:48.00	61	238	47	1	31	0:03:02.00	90	11,9	3,4	81	5,47	1008,00	1,00	315,00	1,00	1	AB001	110,00	-20,00	,00
17	0:16:47.00	61	238	48	1	31	0:03:02.00	91	11,9	3,4	81	5,46	1007,00	1,00	316,00	1,00	1	AB001	110,00	-19,00	,00
18	0:16:46.00	61	238	48	1	31	0:03:02.00	91	11,9	3,4	81	5,46	1006,00	1,00	317,00	1,00	1	AB001	110,00	-19,00	,00
19	0:16:45.00	61	238	48	1	31	0:03:02.00	91	11,9	3,4	81	5,46	1005,00	1,00	318,00	1,00	1	AB001	110,00	-19,00	,00
20	0:16:44.00	61	236	48	1	31	0:03:02.00	91	11,9	3,4	81	5,45	1004,00	1,00	319,00	1,00	1	AB001	110,00	-19,00	,00
21	0:16:43.00	60	238	47	1	31	0:03:05.00	90	11,9	3,4	81	5,44	1003,00	1,00	320,00	1,00	1	AB001	110,00	-20,00	,00
22	0:16:42.00	60	238	47	1	31	0:03:05.00	90	11,9	3,4	81	5,44	1002,00	1,00	321,00	1,00	1	AB001	110,00	-20,00	,00
23	0:16:41.00	60	238	47	1	31	0:03:05.00	90	11,9	3,4	81	5,43	1001,00	1,00	322,00	1,00	1	AB001	110,00	-20,00	,00

Figure 13: Sample database illustrating adherence as a percentage of time spent within the target heart rate range for each subject for each session (horizontal red line highlights the change in adherence between sessions for the same subject).



	Durat.hhmmss_A	Speed Rpm	Caloriecons.Kcalh	HRHR	Level	Watt Watt	Pacemmss km	HRB.M	VO2ml minKg	Mets Mets	Calories Kcal	Distance Km	Tempo	Tempo2	Tempo A	Tempo A2	Session	Subject ID	THR	Diff_HR_THR	Diff_HR_THR_Recoded	Diff_HR_THR_Recoded_mean	Perc_THR
416	0:10:08.00	66	332	55	3	62	0:02:48.00	105	16,8	4,8	45	3,17	608,00	1,00	715,00	1,00	1	AB001	110,00	-5,00	1,00	,70	69,58
417	0:10:07.00	66	328	55	3	62	0:02:48.00	105	16,8	4,8	45	3,17	607,00	1,00	716,00	1,00	1	AB001	110,00	-5,00	1,00	,70	69,58
418	0:10:06.00	65	328	55	3	61	0:02:50.00	105	16,6	4,7	45	3,16	606,00	1,00	717,00	1,00	1	AB001	110,00	-5,00	1,00	,70	69,58
419	0:10:05.00	64	330	56	3	60	0:02:53.00	106	16,4	4,7	45	3,16	605,00	1,00	718,00	1,00	1	AB001	110,00	-4,00	1,00	,70	69,58
420	0:10:04.00	64	328	56	3	60	0:02:53.00	106	16,4	4,7	45	3,15	604,00	1,00	719,00	1,00	1	AB001	110,00	-4,00	1,00	,70	69,58
421	0:10:03.00	64	330	56	3	60	0:02:53.00	106	16,4	4,7	45	3,14	603,00	1,00	720,00	1,00	1	AB001	110,00	-4,00	1,00	,70	69,58
422	0:10:02.00	64	328	56	3	60	0:02:53.00	106	16,4	4,7	45	3,14	602,00	1,00	721,00	1,00	1	AB001	110,00	-4,00	1,00	,70	69,58
423	0:10:01.00	64	330	56	3	60	0:02:53.00	106	16,4	4,7	45	3,13	601,00	1,00	722,00	1,00	1	AB001	110,00	-4,00	1,00	,70	69,58
424	0:10:00.00	64	332	56	3	60	0:02:53.00	106	16,4	4,7	45	3,13	600,00	1,00	723,00	1,00	1	AB001	110,00	-4,00	1,00	,70	69,58
425	0:36:06.00	64	244	55	1	33	0:02:53.00	104	12,2	3,5	178	12,1	2166,00	1,00	300,00	1,00	2	AB001	110,00	-6,00	,00	,93	92,80
426	0:36:05.00	64	242	55	1	33	0:02:53.00	104	12,2	3,5	178	12,09	2165,00	1,00	301,00	1,00	2	AB001	110,00	-6,00	,00	,93	92,80
427	0:36:04.00	64	244	55	1	33	0:02:53.00	104	12,2	3,5	178	12,09	2164,00	1,00	302,00	1,00	2	AB001	110,00	-6,00	,00	,93	92,80
428	0:36:03.00	64	244	55	1	33	0:02:53.00	104	12,2	3,5	178	12,08	2163,00	1,00	303,00	1,00	2	AB001	110,00	-6,00	,00	,93	92,80
429	0:36:02.00	64	244	55	1	33	0:02:53.00	104	12,2	3,5	178	12,07	2162,00	1,00	304,00	1,00	2	AB001	110,00	-6,00	,00	,93	92,80
430	0:36:01.00	64	244	55	1	33	0:02:53.00	104	12,2	3,5	178	12,07	2161,00	1,00	305,00	1,00	2	AB001	110,00	-6,00	,00	,93	92,80
431	0:36:00.00	64	244	55	1	33	0:02:53.00	104	12,2	3,5	178	12,06	2160,00	1,00	306,00	1,00	2	AB001	110,00	-6,00	,00	,93	92,80
432	0:35:59.00	64	248	55	1	33	0:02:53.00	104	12,2	3,5	177	12,06	2159,00	1,00	307,00	1,00	2	AB001	110,00	-6,00	,00	,93	92,80
433	0:35:58.00	64	246	55	1	33	0:02:53.00	104	12,2	3,5	177	12,05	2158,00	1,00	308,00	1,00	2	AB001	110,00	-6,00	,00	,93	92,80
434	0:35:57.00	65	248	55	1	34	0:02:50.00	104	12,4	3,5	177	12,05	2157,00	1,00	309,00	1,00	2	AB001	110,00	-6,00	,00	,93	92,80
435	0:35:56.00	65	246	55	1	34	0:02:50.00	104	12,4	3,5	177	12,04	2156,00	1,00	310,00	1,00	2	AB001	110,00	-6,00	,00	,93	92,80
436	0:35:55.00	65	248	55	1	34	0:02:50.00	104	12,4	3,5	177	12,03	2155,00	1,00	311,00	1,00	2	AB001	110,00	-6,00	,00	,93	92,80
437	0:35:54.00	65	246	55	1	34	0:02:50.00	105	12,4	3,5	177	12,03	2154,00	1,00	312,00	1,00	2	AB001	110,00	-5,00	1,00	,93	92,80

Figure 14: Sample database illustrating adherence for the percentage of time spent within the target heart rate range for each subject for all sessions (horizontal red line highlights the difference between subjects).



*Group01_Subjects001-010.sav [DataSet1] - IBM SPSS Statistics Data Editor

File Edit View Data Transform Analyze Graphs Utilities Add-ons Window Help

1926 : Durat.hhmmss_A 0:11:05.00 Visible: 23 of 23 Variables

	Durat.hhmmss_A	Speed Rpm	Caloriecons.Kcalh	HRHR	Level	Watt Watt	Pacemmss km	HRB.M	VO2ml minKg	Mets Mets	Calories Kcal	Distance Km	Tempo	Tempo2	Tempo A	Tempo A2	Session	Subject ID	THR	Diff_HR_THR	Diff_HR_THR_Recoded	Diff_HR_THR_Recoded_mean	Perc_THR_per_subject
1981	0:10:10....	66	336	55	3	62	0:02:48.00	104	16,8	4,8	46	3,21	610,00	1,00	1856,0	1,00	36	AB001	110,00	-6,00	,00	,87	87,34
1982	0:10:09....	66	332	55	3	62	0:02:48.00	104	16,8	4,8	46	3,21	609,00	1,00	1857,0	1,00	36	AB001	110,00	-6,00	,00	,87	87,34
1983	0:10:08....	66	328	55	3	62	0:02:48.00	104	16,8	4,8	46	3,2	608,00	1,00	1858,0	1,00	36	AB001	110,00	-6,00	,00	,87	87,34
1984	0:10:07....	65	328	55	3	61	0:02:50.00	104	16,6	4,7	46	3,2	607,00	1,00	1859,0	1,00	36	AB001	110,00	-6,00	,00	,87	87,34
1985	0:10:06....	64	330	55	3	60	0:02:53.00	104	16,4	4,7	45	3,19	606,00	1,00	1860,0	1,00	36	AB001	110,00	-6,00	,00	,87	87,34
1986	0:10:05....	64	370	55	3	60	0:02:53.00	104	16,4	4,7	45	3,18	605,00	1,00	1861,0	1,00	36	AB001	110,00	-6,00	,00	,87	87,34
1987	0:10:04....	64	370	55	3	60	0:02:53.00	104	16,4	4,7	45	3,18	604,00	1,00	1862,0	1,00	36	AB001	110,00	-6,00	,00	,87	87,34
1988	0:10:03....	64	370	55	3	60	0:02:53.00	104	16,4	4,7	45	3,18	603,00	1,00	1863,0	1,00	36	AB001	110,00	-6,00	,00	,87	87,34
1989	0:10:02....	64	366	55	4	73	0:02:53.00	104	18,5	5,3	45	3,17	602,00	1,00	1864,0	1,00	36	AB001	110,00	-6,00	,00	,87	87,34
1990	0:10:01....	63	364	55	4	72	0:02:56.00	104	18,3	5,2	45	3,17	601,00	1,00	1865,0	1,00	36	AB001	110,00	-6,00	,00	,87	87,34
1991	0:10:00....	63	364	55	4	72	0:02:56.00	104	18,3	5,2	45	3,17	600,00	1,00	1866,0	1,00	36	AB001	110,00	-6,00	,00	,87	87,34
1992	0:17:18....	49	218	60	1	25	0:03:46.00	114	10,9	3,1	63	5,14	1038,00	1,00	300,00	1,00	1	CD002	115,00	-1,00	1,00	,91	91,12
1993	0:17:17....	49	220	60	1	25	0:03:46.00	114	10,9	3,1	63	5,13	1037,00	1,00	301,00	1,00	1	CD002	115,00	-1,00	1,00	,91	91,12
1994	0:17:16....	49	218	60	1	25	0:03:46.00	114	10,9	3,1	63	5,13	1036,00	1,00	302,00	1,00	1	CD002	115,00	-1,00	1,00	,91	91,12
1995	0:17:15....	49	218	60	1	25	0:03:46.00	114	10,9	3,1	63	5,13	1035,00	1,00	303,00	1,00	1	CD002	115,00	-1,00	1,00	,91	91,12
1996	0:17:14....	50	222	60	1	25	0:03:42.00	114	10,9	3,1	63	5,12	1034,00	1,00	304,00	1,00	1	CD002	115,00	-1,00	1,00	,91	91,12
1997	0:17:13....	51	222	60	1	26	0:03:37.00	114	11,1	3,2	63	5,11	1033,00	1,00	305,00	1,00	1	CD002	115,00	-1,00	1,00	,91	91,12
1998	0:17:12....	51	222	59	1	26	0:03:37.00	113	11,1	3,2	63	5,11	1032,00	1,00	306,00	1,00	1	CD002	115,00	-2,00	1,00	,91	91,12
1999	0:17:11....	51	224	59	1	26	0:03:37.00	113	11,1	3,2	63	5,1	1031,00	1,00	307,00	1,00	1	CD002	115,00	-2,00	1,00	,91	91,12
2000	0:17:10....	52	226	59	1	26	0:03:33.00	113	11,1	3,2	63	5,1	1030,00	1,00	308,00	1,00	1	CD002	115,00	-2,00	1,00	,91	91,12
2001	0:17:09....	52	226	59	1	26	0:03:33.00	113	11,1	3,2	63	5,1	1029,00	1,00	309,00	1,00	1	CD002	115,00	-2,00	1,00	,91	91,12
2002	0:17:08....	53	224	59	1	27	0:03:29.00	113	11,3	3,2	63	5,09	1028,00	1,00	310,00	1,00	1	CD002	115,00	-2,00	1,00	,91	91,12

Data View Variable View

IBM SPSS Statistics Processor is ready

EN 10:29

DISCUSSION:

Continuous data tracking technology enables for a very precise measurement of exercise adherence. This procedure can be easily adapted to other definitions of adherence by replacing target heart rate range with target wattage, level, speed, or MET level. In the present example, the warm-up and cool-down phases were eliminated to isolate the exercise phase because of our specific research objective. Should the warm-up and cool-down phases be of interest to other researchers, step 2.4 (“Eliminate the non-training phases”) can be eliminated from the protocol. Furthermore, the hardware

and software is also available to measure adherence to other modes of training, such as the treadmill, elliptical, stepper, and arm ergometer.

When following the above protocol, certain simple steps are critical. First, the CardioMemory software must be started before the exercise equipment (e.g. cycle ergometer) for exercise data to be tracked and subsequently recorded. Should data be lost at this initial step, the data extraction protocol will need to be adjusted accordingly. Secondly, sources of interference must be minimized to reduce the risk of crosstalk and/or lost data. The heart rate monitors communicate wirelessly with the equipment and software. Thus, interference is especially detrimental if using target heart rate to calculate adherence. Finally, it is imperative to select statistical software for the database that has the capacity to permit for large quantities of data. For example, in a study with 10 participants completing 36 sessions at 40 minutes each, 864 000 rows of data points will be generated. Excel 2007 and later versions have the capacity to contain 1,048,576 rows in a worksheet[23], whereas SAS[24] and SPSS[25] have no limit for the number of rows. Depending on the total number of data points expected for a given study, the software needs to be selected accordingly.

Despite the notable advantages of this technology, two main limitations exist. The first is data loss, which can result from equipment and/or software failure. As mentioned above, data loss can be due to electrical interference with wireless devices (i.e., cell phones or WiFi), and more specifically interference with the wireless data transmission of heart rate. However, at times, data loss can also be due to unidentifiable causes. A second limitation is that the software does not provide the option of marking or

splitting the exercise protocol systematically in order to differentiate/identify different phases. If this option were available, the extraction of the exercise phase of interest could be performed directly in the software, which would limit steps in the adherence calculation protocol. As well, the option of placing markers would be practical for the study of adherence to interval or intermittent training protocols as it would allow for the differentiation of the different phases (e.g. low versus high intensity).

For future perspectives, the use of continuous data tracking technology to precisely quantify adherence will enable researchers to investigate patterns of exercise response to different interventions, identify determinants of adherence, and characterize good and poor adherers. Ultimately, a better understanding of exercise adherence will allow for the optimization of exercise rehabilitation programs.

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manuscript and video. V. Pepin participated in the development of the protocol, the writing of the manuscript, the filming of the video, secured funding for the project, and critically revised the manuscript and video.

DISCLOSURES: The authors declare that they have no competing financial interests.

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8. APPENDIX B: Manuscript - Acute Responses to Different Exercise-Training Protocols and Relationship with Adherence to Pulmonary Rehabilitation in COPD (submitted to Thorax Feb. 2014)

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Keywords: Chronic obstructive pulmonary disease, exercise, physiology, affect, patient compliance.

What is the key question? Do immediate responses to exercise-training protocols influence subsequent adherence to pulmonary rehabilitation, and does affect/vigor mediate or moderate the relationship between exercise intensity and adherence in COPD?

What is the bottom line? Exercise-training intensity, more specifically VO2, is negatively related to 12-week adherence in COPD, but this relationship may be moderated by end-exercise vigor.

Why read on? This is the first study to investigate acute responses to different exercise training protocols and subsequent relationship to exercise adherence in COPD.

ABSTRACT

Objectives: i) Compare, in COPD patients, the acute physiological, symptomatic, and affective responses to continuous training at a high-intensity (CTHI), continuous training at the ventilatory threshold (CTVT), and interval training (IT); ii) Examine the association between acute responses and 12-week adherence to training; iii) Investigate whether the relationship between acute responses and adherence is mediated/moderated by affect/vigor.

Methods: Thirty-five COPD patients (FEV_1 = 60.2±15.8 % predicted) underwent baseline assessments, were randomly assigned to CTHI, CTVT, or IT, were precisely monitored throughout an entire exercise-training bout, and underwent 12 weeks of training during which adherence was continuously tracked.

Results: Compared to CTHI, CTVT was associated with a lower exercise RER, HR, and RR, while IT induced a higher $\dot{V}_E$, $\dot{V}_E$/MVV, RR, and a greater drop in SpO_2. From pre- to post-exercise, positive affect increased (F=9.74, p<0.001) and negative affect decreased (F=6.43, p=0.005) across groups. The CTVT group reported greater end-exercise vigor compared to CTHI (p=0.01) and IT (p=0.02). The IT group exhibited the lowest post-exercise vigor (p=0.04 versus CTHI and p=0.02 versus CTVT) and 12-week adherence rate (F=6.69, p=0.004). Mean exercise $\dot{V}O_2$ (r=-0.466, p=0.007) and end-exercise vigor (r=0.420, p=0.017) were most strongly correlated with adherence. End-exercise vigor moderated the relationship between $\dot{V}O_2$ and adherence (β=2.74, t(32)=2.32, p=0.03).

Conclusion: Mean exercise $\dot{V}O_2$, measured during an exercise-training bout at the beginning of pulmonary rehabilitation, was inversely related to 12-week exercise

adherence in COPD, possibly supportive of an intensity-adherence trade-off. This relationship may be moderated by the level of vigor reported by patients at end-exercise.

INTRODUCTION

Exercise training is a key component to successful pulmonary rehabilitation (PR)[213]. Current PR guidelines advocate continuous training at a high-intensity (CTHI) for patients with chronic obstructive pulmonary disease (COPD)[213, 214]. However, a major issue with the use of CTHI is the associated low adherence rates[164]. Alternative approaches, including continuous training at the ventilatory threshold (CTVT) and interval training (IT), have therefore been proposed as more tolerable and likely to be associated with better long-term adherence[115-117, 213].

The acute response to different exercise-training protocols has been examined in COPD from physiological and symptomatic perspectives. Compared to CTHI, IT has been associated with less physiological strain [lower oxygen uptake ($\dot{V}O_2$), carbon dioxide excretion ($\dot{V}CO_2$), minute ventilation ($\dot{V}_E$), and heart rate (HR)], less or similar degrees of dynamic hyperinflation, less dyspnoea, and greater total amount of work or endurance time achieved[115, 117]. CTVT has been associated with lower $\dot{V}CO_2$ and $\dot{V}_E$ for a given workload (W) compared to continuous training at a standardized moderate intensity (50% HR reserve)[116]. However the link between acute responses to these protocols and subsequent adherence remains to be established.

In healthy individuals, evidence suggests that exercise intensity is negatively related to long-term adherence[211, 212]. This relationship is thought to be driven by

affect – the degree of pleasure/displeasure one experiences during exercise – especially during the initial phase of an exercise program[196]. Lower intensities are thought to be more enjoyable, leading to better adherence[203]. During exercise, affect has been negatively related to physiological responses of metabolic strain[203, 215]. More detailed studies have suggested that affect improves or remains stable when intensities are below or at the ventilatory threshold[196, 207, 216, 217], and worsens above the ventilatory threshold[196, 197, 207, 216-219]. Accordingly, affect should remain stable or improve during CTVT and, possibly as well, during IT because of the regular recovery periods; in contrast, it can be hypothesized that affect would worsen during CTHI, which continuously submits patients to intensities above the ventilatory threshold, and that this approach would be associated with lower adherence than CTVT and IT.

The objectives of this study were to: i) compare, in COPD, the acute physiological, symptomatic, and affective responses to CTHI, CTVT, and IT; ii) examine the association between acute responses and adherence to a 12-week exercise-training program; and iii) investigate whether the relationship between acute responses and adherence is mediated/moderated by affect/vigor.

METHODS

Study Design and Procedure

This was a sub-study to a larger randomized clinical trial (NCT01933308). Eligible subjects completed baseline evaluations, were randomly assigned to one of

three protocols, were monitored throughout an entire exercise-training bout, and underwent 12 weeks of training, 3 times/week, according to the assigned protocol (details in online supplement). Both sub-study and larger trial were approved by the institutional ethics committee and signed informed consents were obtained for each study.

Subjects

Subjects were recruited at l'Hôpital du Sacré-Coeur de Montréal according to the following criteria: *Inclusion*: 1) COPD diagnosis; 2) age ≥ 40 years; 3) smoking history ≥ 10 American pack-years; 4) post-bronchodilation forced expiratory volume in one second (FEV_1) < 80% of predicted normal value; and 5) FEV_1 to forced vital capacity (FVC) ratio < 0.7. *Exclusion*: 1) exacerbation of respiratory symptoms ≤ 4 weeks; 2) contraindication to exercise testing[214]; 3) active condition other than COPD that can influence exercise tolerance; 4) resting or exercising oxygen therapy; 5) participation in a PR program ≤ 1 year; 6) participation in a current exercise-training program of similar or greater dose than protocols under study[220]; and 7) inability to complete baseline evaluations or to achieve a ventilatory threshold on the incremental cycling test.

Baseline Assessments

Expiratory flow rates, lung volumes, and lung diffusion capacity were measured according to recommended techniques[179]. Values were compared to predicted normal values from the European Community for Coal and Steel/European Respiratory Society[193]. A symptom-limited incremental cycling test was performed to rule out the presence of cardiovascular co-morbidities and assess W at peak effort (highest W

maintained at ≥ 50 revolutions/minute for ≥ 30 seconds) and at the ventilatory threshold (determined using V-slope method[182]) for subsequent determination of exercise-training intensity[181] (details in online supplement).

Exercise-Training Protocols

Exercise training was performed on cycle ergometers at the hospital's cardiopulmonary rehabilitation centre. Training included a 10-minute warm-up (5 minutes unloaded and 5 minutes at progressively increasing load), an intensity phase at subjects' respective target intensity and duration, and a 5-minute cool-down. The intensity phase for CTHI consisted of 25 minutes of pedalling at the HR reached at 80% of Wpeak on the incremental test. For CTVT, the target intensity was the HR reached at the ventilatory threshold, while IT consisted of 30-second intervals at the HR reached at 100% Wpeak interspersed with 30-second intervals of unloaded pedalling. Session duration for CTVT and IT was adjusted for each subject using metabolic equations[221] to equal total amount of work performed to 25 minutes of CTHI. Subjects were instructed to train within ±5 beats/minute of the target HR identified. Two trained exercise physiologists supervised sessions; instructions and feedback were standardized.

Acute Response to Exercise Training

Acute response to training was measured during an entire bout in the beginning phase of the PR program (-1 week to +2 weeks of start). Physiological measurements [$\dot{V}O_2$, $\dot{V}CO_2$, respiratory exchange ratio (RER), $\dot{V}_E$, tidal volume (V_T), respiratory rate (RR), pulse oxygen saturation (SpO_2)] were continuously recorded throughout the bout using portable equipment (Oxycon Mobile, Jaeger, Germany). Inspiratory capacities (IC)

were measured every 5 minutes, as were perceived dyspnoea and leg fatigue using the modified 10-point Borg scale[222]. Affect was measured using the Positive and Negative Affect Schedule (PANAS)[136] and Global Vigor and Affect (GVA) instrument[144] (details in online supplement).

Adherence to Exercise-Training Program

Adherence was defined as percent time spent within the target heart rate range throughout the 12-week program and measured for attended sessions using continuous data tracking technology (Bike Excite Med 700, Technogym, Italy; T31 transmitter, Polar, Finland; CardioMemory, Technogym, Italy). A detailed description of this methodology has been published[223]. Since subjects undergoing IT were expected to spend 50% of their time in their target heart rate range (during high intervals), adherence for this group was obtained by multiplying the time spent within the target heart rate range by two up to a maximum of 100%.

Statistical Analyses

Baseline measurements were compared between groups using one-way analyses of variance (ANOVA). Acute physiological and symptomatic changes to exercise were analyzed with a series of repeated-measures mixed models. To assess the acute effects of exercise protocols on PANAS (positive and negative affect) and GVA (global affect and vigor) responses, four repeated-measures general linear models were conducted. Mean adherence to the intervention protocols was compared using Levene's test (details in online supplement). Adherence data lost from technical difficulties were replaced by bringing the last value forward. To assess the intensity-adherence

relationship, associations between a priori selected acute measures [W, $\dot{V}O_2$ (L/min), $\dot{V}O_2$ (% peak), $\dot{V}O_2$ (% ventilatory threshold), HR (beats/min), $\dot{V}_E$ (L/min), IC/TLC, dyspnoea, leg fatigue, global affect (50% and 100%), and global vigor (50% and 100%)] and 12-week adherence rates were identified using Partial correlations, adjusting for attendance rate. It was a priori decided that a maximum of 1 correlate per 10 subjects would be retained for further analysis, after ensuring absence of multicollinearity ($r > \pm 0.7$) between correlates[190]. The role of affect and vigor as potential mediators or moderators in the intensity-adherence relationship was assessed using Preacher and Hayes[191] and Hayes's approach[192] respectively, adjusting for attendance rate. Analyses were performed using SAS (v9.1, SAS Institute, Cary NC) and p-value was set at 0.05.

RESULTS

Subjects

Baseline characteristics are presented in Table 1. Thirty-five subjects completed the acute bout. The sample was predominantly composed of female (60%) and overweight (66%) participants with, on average, moderate-to-severe airflow obstruction corresponding to GOLD stage II-III COPD[1], significant resting lung hyperinflation and parenchymal destruction. No significant between-group differences were found for baseline characteristics.

Enter Table 1 around here.

Response to the symptom-limited incremental cycling test are presented in Table 2. Subjects had, as expected, reduced peak W, HR, and $\dot{V}O_2$ compared to normal predicted values, but a relatively preserved exercise tolerance for a COPD population. No significant between-group differences were observed, except for peak $\dot{V}_E$/maximal voluntary ventilation (MVV), which was significantly lower in CTVT than IT, suggesting that subjects in CTVT were either less ventilatory limited or further away from maximal effort than those in IT.

Enter Table 2 around here.

Acute Responses to Exercise Training

Everyone, except one subject from CTHI, achieved the target exercise duration (Table 3). The time course for absolute and relative physiological parameters for which significant between-group differences were observed are found in Figures 1 and 2, respectively (additional graphs in online supplement). Symptomatic responses are shown in Figure 3. PANAS results revealed a significant time effect from rest to post-exercise for positive ($F=9.74$, $p<0.001$) and negative ($F = 6.43$, $p = 0.005$) affect scores, but no time by intervention group interaction (Figure 4). GVA results indicated a significant time effect from rest to post-exercise for both global affect ($F = 8.47$, $p < 0.001$) and vigor ($F = 9.79$, $p < 0.001$) (Figure 5). Additionally, a time by intervention group interaction was observed. For global affect, CTVT scored less than other groups at 50% of exercise time; the difference was significant against CTHI ($p = 0.04$) and approached significance against IT ($p = 0.06$). For global vigor, CTVT scored significantly higher than CTHI ($p = 0.01$) and IT ($p = 0.02$) at 100% of exercise time (i.e.

end-exercise), while IT scored significantly less than CTHI (p = 0.04) and CTVT (p = 0.02) 30-minutes post-exercise.

Enter Table 3 around here.

Adherence to Exercise-Training Program

One subject from CTHI was excluded after completing the acute bout for medical reasons. Mean attendance was not significantly different between groups [CTHI: 70.1 ± 32.9% (range: 49.3-91.0); CTVT: 81.9 ± 17.2% (range: 71.0-92.9); IT: 73.3 ± 28.6% (range: 52.9-93.8), F = 0.61, p = 0.55]. Mean 12-week adherence to the target HR was significantly lower in IT compared to CTHI and IT [CTHI: 85.6 ± 15.0% (range: 76.0-95.1); CTVT: 85.4 ± 15.8% (range: 75.3-95.5); IT: 49.0 ± 42.8% (range: 18.4-79.7), F = 6.69, p = 0.004]. Standardization attempts failed to normalize adherence data; thus, original values were used.

Relationship Between Acute Responses and Adherence

After adjusting for percent attendance rate, mean achieved W (r = -0.429, p = 0.014), $\dot{V}O_2$ (L/min) (r = -0.466, p = 0.007), $\dot{V}_E$ (L/min) (r = -0.463, p = 0.008), and end-exercise global vigor (r = 0.420, p = 0.017) were most strongly correlated with adherence. Multicolinearity was found between $\dot{V}O_2$ (L/min) and $\dot{V}_E$ (L/min) (r = 0.771, p < 0.001) and between $\dot{V}O_2$ (L/min) and W (r = 0.832, p < 0.001). Variables retained as

the strongest correlates of adherence were mean $\dot{V}O_2$ (L/min) and end-exercise global vigor.

The mediation model was not supported by our data (details in online supplement). When moderation was tested with $\dot{V}O_2$ as the predictor, end-exercise global vigor as the moderator, and adherence as the outcome (Figure 6), the product of $\dot{V}O_2$ and end-exercise global vigor was significant (β = 2.74, t(32) = 2.32, p = 0.03) indicating that vigor moderates the relationship between $\dot{V}O_2$ and exercise adherence. Using the Johnson-Neyman technique, a cut-off value of 77 was identified, above which global vigor acted as a significant moderator (Figure 7). Above a vigor score of 77, the intensity-adherence relationship weakened.

DISCUSSION

The present study findings can be summarized as follows: i) affect generally improved from rest to post-exercise; ii) CTVT was less physiologically demanding than CTHI and IT, was associated with a more pronounced drop in global affect mid-exercise, but with less leg fatigue and better end-exercise vigor; iii) IT was associated with a more pronounced ventilatory response than CTHI and CTVT, lower levels of alertness post-exercise, and reduced 12-week adherence; iv) acute mean $\dot{V}O_2$, was most strongly and inversely related to 12-week adherence; and v) this relationship was moderated by end-exercise vigor.

Results on the acute physiological response to IT compared to CTHI differ from previous reports, showing reduced metabolic strain with IT compared to CTHI[115, 117]. Inconsistencies between our results and those from Sabapathy and colleagues[115] are likely attributable to disparities in IT protocols. In our study, IT consisted of shorter intervals (30 seconds versus 1 minute) of a higher relative intensity (100% versus 70% Wpeak) alternated with active recovery (versus rest). These differences likely translated into less time for recovery with our IT protocol, thereby making it more physiologically demanding. As for Vogiatzis et al.[117], our findings possibly differed from theirs due to disparities in the continuous training protocols. Their subjects were asked to maintain a wattage corresponding to 80% Wpeak[117]; in the present study, subjects were asked to remain within a ± 5 beats/min of the HR reached at 80% Wpeak on the incremental test, corresponding to approximately 60% Wpeak. Thus, our CTHI protocol was less physiologically demanding than theirs. It seems reasonable to conclude that depending on the protocols used, IT can be similarly, slightly more, or slightly less physiologically demanding than CTHI. Also, based on the present study, IT may be associated with lower levels of alertness post-exercise.

Comparing CTHI and CTVT, our results support Vallet et al.'s[116] findings suggesting that CTVT is more tolerable physiologically for COPD patients than continuous training at a standardized intensity. CTVT was also shown, for the first time in COPD, to be associated with higher levels of end-exercise alertness. This approach may thus be associated with better long-term adherence than CTHI and IT. CTVT was associated with less leg fatigue, but the difference disappeared when expressed as a percentage of peak. Furthermore, CTVT was not associated with reduced dyspnoea, as

previously reported by Vallet et al.[116]. Ratings of perceived breathlessness have previously been suggested as unresponsive to increases in exercise performance[194] and declines in lung function over time[195]. The presence of a dyspnoea threshold in COPD has been proposed, that when surpassed may not be well tolerated[194]. Subjects may therefore consciously or unconsciously select a level of dyspnoea not to surpass[194]. Our findings may reflect this phenomenon.

Positive changes in affective state (increase in positive and/or global affect, and decrease in negative affect) observed from rest to post-exercise across training protocols is consistent with previous findings in healthy populations, which show acute exercise-induced improvements in affect with varying training intensities[196, 197, 216]. However, our group results are not in line with the contention that affect improves or remains stable during exercise performed at the ventilatory threshold, and worsens when the intensity is above the ventilatory threshold. Indeed, CTVT, which exercised at 100% of its ventilatory threshold (Table 3), experienced the greatest dip in affect mid-exercise, while CTHI and IT, which exercised above their ventilatory threshold (109% and 108%, respectively; Table 3), experienced less or no dip. Perhaps COPD patients, who face discomfort on a regular basis, react differently than healthy individuals to different exercise intensities. Elevated rates of psychological and cognitive impairments have been documented in COPD[201, 224]. These factors have been shown to variably alter the affective response to exercise; this may explain discrepancies between our findings and those in healthy individuals[203, 215].

In the present study, adherence to the different protocols was measured using continuous data tracking technology. Using this precise measure, subjects from the IT group were found to have spent a significantly lower percentage of time at the target intensity (49%) compared to CTHI (86%) and CTVT (85%). This finding, however, needs to be interpreted with caution since this study was not powered to detect differences in adherence rates between protocols. Rather, it emphasized on the relationship between acute responses and subsequent adherence to different protocols to validate/invalidate previously proposed conceptual models from healthy populations. To that extent, our results suggest that acute measures of exercise intensity, more specifically $\dot{V}O_2$, is most strongly and negatively related to 12-week adherence, possibly suggestive of an intensity-adherence trade-off, as previously observed in healthy individuals[211, 212]. Furthermore, end-exercise vigor was found to moderate this relationship. A cut-off value of 77 was identified, above which end-exercise vigor weakened the intensity-adherence relationship. This suggests that, if end-exercise vigor remains above this value, higher intensities may not be associated with lower adherence rates. Measuring end-exercise vigor during the beginning phase of a PR program may thus provide valuable clinical insight.

This study needs to be interpreted in the context of some limitations. Sample size was small, which may have affected our power, and our groups were unequal in size. Furthermore, based on the general response to the incremental cycling test, it is likely that the test was symptom-limited, as opposed to maximal, in a number of subjects. A submaximal test translates into an under-estimated exercise prescription, where subjects may have trained below targeted intensities. Adherence rates were also high

and slightly negatively skewed, which may have biased the interpretation of that data. Finally, given the demands of the trial, a recruitment bias towards highly motivated individuals may have occurred, limiting the generalizability of our findings.

In conclusion, CTVT was associated with less physiological strain and higher levels of end-exercise alertness compared to CTHI and IT in participants with moderate-to-severe airflow obstruction. Mean exercise $\dot{V}O_2$, measured during an exercise-training bout at the beginning of pulmonary rehabilitation, was inversely related to 12-week adherence, possibly supportive of an intensity-adherence trade-off. This relationship may be moderated by the level of vigor reported by patients at end-exercise.

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Table 1. Baseline characteristics of the study groups.

	CTHI (n = 13)	**CTVT** (n = 12)	**IT** (n = 10)	**p-value**
Male/Female, n	4/9	6/6	4/6	0.368
Age, years	66.3 ± 6.7	69.3 ± 8.9	66.8 ± 11.2	0.671
BMI, kg/m^2	28.3 ± 4.9	27.1 ± 5.4	28.3 ± 5.4	0.819
Smoking, pack-years	48.7 ± 17.0	47.5 ± 14.4	33.2 ± 18.1	0.159
Pulmonary Function				
FEV_1, L	1.41 ± 0.32	1.61 ± 0.42	1.28 ± 0.50	0.181
FEV_1, % predicted	59.7 ± 14.5	66.2 ± 16.7	53.8 ± 14.9	0.182
FVC, L	2.77 ± 0.59	3.20 ± 0.59	2.57 ± 0.83	0.089
FVC, % predicted	94.2 ± 15.8	105.6 ± 24.1	87.9 ± 21.6	0.136
FEV_1/FVC, %	51.9 ± 11.1	50.4 ± 9.5	49.1 ± 6.1	0.775
TLC, L	5.93 ± 1.57	6.57 ± 1.62	5.66 ± 0.85	0.311
TLC, % predicted	107.8 ± 21.9	113.0 ± 18.6	106.1 ± 15.5	0.672
FRC, L	3.93 ± 1.22	4.28 ± 1.19	3.84 ± 0.60	0.582
FRC, % predicted	131.1 ± 34.5	136.3 ± 27.5	129.9 ± 17.4	0.846
RV, L	2.96 ± 1.01	3.15 ± 1.18	2.94 ± 0.60	0.857
RV, % predicted	136.1 ± 42.3	135.8 ± 40.9	139.3 ± 33.5	0.976
D_LCO, % predicted	54.4 ± 8.1	53.1 ± 12.8	54.5 ± 10.6	0.937

Values presented are Mean ± SD. CTHI: continuous training at a high intensity; CTVT: continuous training at the ventilatory threshold; IT: interval training; BMI: body mass index; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; TLC: total lung capacity; FRC: functional residual capacity; RV: residual volume; D_LCO: lung diffusion capacity for carbon monoxide.

Table 2. Responses to symptom-limited incremental cycling test for each group.

	CTHI (n = 13)	**CTVT** (n = 12)	**IT** (n = 10)	**p-value**
Peak Responses				
Workload, W	65.8 ± 15.5	72.1 ± 24.8	69.0 ± 28.0	0.789
Workload, % predicted	59.6 ± 18.4	59.7 ± 15.9	62.9 ± 25.9	0.913
HR, beats/min	117.9 ± 16.7	123.1 ± 19.1	124.5 ± 18.1	0.645
HR, % predicted	77.5 ± 11.4	80.8 ± 11.7	80.8 ± 10.3	0.704
$\dot{V}O_2$, L/min	1.02 ± 0.19	1.07 ± 0.40	1.13 ± 0.39	0.738
$\dot{V}O_2$, ml/kg/min	13.43 ± 2.92	14.03 ± 3.75	14.83 ± 3.16	0.606
$\dot{V}O_2$, % predicted	80.4 ± 32.6	74.6 ± 28.8	86.2 ± 28.3	0.671
$\dot{V}CO_2$, L/min	1.07 ± 0.25	1.11 ± 0.39	1.22 ± 0.48	0.623
RER	1.05 ± 0.10	1.04 ± 0.05	1.07 ± 0.12	0.743
RR, breaths/min	33.3 ± 5.9	32.7 ± 5.1	34.6 ± 3.5	0.665
$\dot{V}_E$, L/min	40.36 ± 7.19	41.81 ± 14.13	41.63 ± 14.42	0.949
$\dot{V}_E$ / MVV	0.85 ± 0.19	0.75 ± 0.18	0.95 ± 0.13	0.033
SpO_2, %	94.9 ± 2.9	93.7 ± 2.2	94.2 ± 2.2	0.474
Dyspnoea, Borg	7.0 ± 2.1	6.4 ± 2.0	7.9 ± 1.9	0.236
Leg fatigue, Borg	7.8 ± 1.8	6.7 ± 2.3	7.8 ± 2.3	0.332
Responses at the VT				
Workload at VT, W	33.9 ± 18.3	37.5 ± 9.4	33.0 ± 20.6	0.788
Workload at VT, % peak	51.9 ± 27.6	54.4 ± 11.8	48.7 ± 26.4	0.848
HR at VT, beats/min	99.8 ± 13.7	100.7 ± 12.8	103.7 ± 9.5	0.740
HR at VT, % peak	83.9 ± 7.0	82.6 ± 8.6	84.3 ± 9.1	0.874
$\dot{V}O_2$ at VT, L/min	0.72 ± 0.14	0.74 ± 0.20	0.79 ± 0.19	0.658
$\dot{V}O_2$ at VT, ml/kg/min	9.42 ± 1.67	9.80 ± 1.98	10.60 ± 2.66	0.408
$\dot{V}O_2$ at VT, % peak	71.5 ± 12.7	71.8 ± 9.9	71.6 ± 8.6	0.998
$\dot{V}CO_2$ at VT, L/min	0.63 ± 0.12	0.66 ± 0.14	0.71 ± 0.17	0.469
$\dot{V}CO_2$ at VT, % peak	61.2 ± 15.9	62.0 ± 10.8	61.0 ± 10.9	0.983
RER at VT	0.88 ± 0.10	0.82 ± 0.27	0.90 ± 0.07	0.556
RR at VT, breaths/min	24.0 ± 4.4	23.5 ± 7.5	27.6 ± 3.2	0.183

RR at VT, % peak	73.9 ± 16.0	72.3 ± 20.3	80.1 ± 8.3	0.503
$\dot{V}_E$ at VT, L/min	24.80 ± 5.00	25.92 ± 7.58	27.86 ± 5.98	0.513
$\dot{V}_E$ at VT, % peak	63.5 ± 17.3	63.2 ± 9.8	70.9 ± 16.4	0.409
SpO_2 at VT, %	95.2 ± 1.9	94.4 ± 1.8	94.8 ± 1.9	0.520
SpO_2 at VT, % peak	100.4 ± 2.4	100.8 ± 1.6	100.6 ± 1.1	0.874

Values presented are Mean ± SD. CTHT: continuous training at a high intensity; CTVT: continuous training at the ventilatory threshold; IT: interval training; VT: ventilatory threshold; HR: heart rate; $\dot{V}O_2$: oxygen uptake; $\dot{V}CO_2$: carbon dioxide excretion; RR: respiratory rate; $\dot{V}_E$: minute ventilation; MVV: maximal voluntary ventilation; RER: respiratory exchange ratio; SpO_2: pulse oxygen saturation.

Table 3. Target and achieved response to acute exercise bout during the intensity phase of training for CTHI, CTVT, and IT.

	CTHI (n = 13)	**CTVT** (n = 12)	**IT** (n = 10)	**p-value**
Target				
Duration, min	25.0 ± 0	30.7 ± 2.9	31.5 ± 1.2	< 0.001
HR, bpm	109.1 ± 15.2	101.5 ± 12.2	125.2 ± 13.5*	0.001
Achieved				
Duration, min	24.2 ± 2.8	30.7 ± 2.9	31.5 ± 1.2	< 0.001
HR, bpm	109.0 ± 16.2	101.3 ± 11.4	112.2 ± 14.5**	0.187
HR, % target	99.9 ± 3.5	99.8 ± 2.4	89.6 ± 7.2**	< 0.001
HR, % peak	91.4 ± 4.8	83.1 ± 7.3	90.6 ± 7.9	0.008
HR, % VT	109.3 ± 7.0	100.8 ± 2.9	108.0 ± 7.4	0.003

Values presented are mean ± SD.
CTHI: continuous training at a high intensity; CTVT: continuous training at the ventilatory threshold; IT: interval training; HR: heart rate; VT: ventilatory threshold.
***** = target for the high interval (no specific target for the low interval)
****** = average of high and low interval
[#] = analyzed in 34 individuals

FIGURE LEGENDS

Figure 1 Time course values for $\dot{V}O_2$ in L/min (A), $\dot{V}CO_2$ (L/min) (B), RER (C), $\dot{V}_E$ /MVV (D), RR (breaths/min) (E), and IC (L) (F) for CTHI (black circles), CTVT (white circles), and IT (grey circles). Depicted timescales include 10-minute warm-up. Achieved values for the IT group represent the average of the high and low intervals. For the CTHI group, n = 34 after 25 minutes. Values are mean. * = significant between-group difference at $p<0.05$.

Figure 2 Time course values for RER (% peak) (A), HR (% peak) (B), $\dot{V}_E$ (% peak) (C), $\dot{V}_E$ /MVV (% peak) (D), RR (% peak) (E), SpO_2 (% change from rest) (F) for CTHI (black circles), CTVT (white circles), and IT (grey circles). Depicted timescales include 10-minute warm-up. Achieved values for the IT group represent the average of the high and low intervals. Values are mean. For the CTHI group, n = 34 after 25 minutes. * = significant between-group difference at $p<0.05$.

Figure 3 Dyspnoea and leg fatigue as measured by the modified 10-Point Borg scale for CTHI (black circles), CTVT (white circles), and IT (grey circles). Depicted timescales begin with the first minute 5 measurement. For the CTHI group, n = 34 after 25 minutes. Values are mean. * = significant between-group difference at $p<0.05$.

Figure 4 Positive and negative affect, as measured by the PANAS, for CTHI (black circles), CTVT (white circles), and IT (grey circles). † = significant difference at $p<0.001$. * = significant difference at $p<0.01$.

Figure 5 Global affect and global vigor, as measured by the GVA, for CTHI (black circles), CTVT (white circles), and IT (grey circles). † = significant difference at $p<0.001$.

= significant difference from CTHI at p<0.05. * = significant difference from other groups at p<0.05.

Figure 6 Conceptual moderation model (A) and statistical moderation model (B) with $\dot{V}O_2$ as the predictor (independent variable), global vigor at end-exercise as the moderator, and adherence as the outcome (dependent variable) while adjusting for attendance.

Figure 7 Predicted adherence against $\dot{V}O_2$ for three levels of end-exercise global vigor. $\hat{Y}$: predicted adherence; X: mean $\dot{V}O_2$; M: moderator.

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FIGURES

Figure 1.

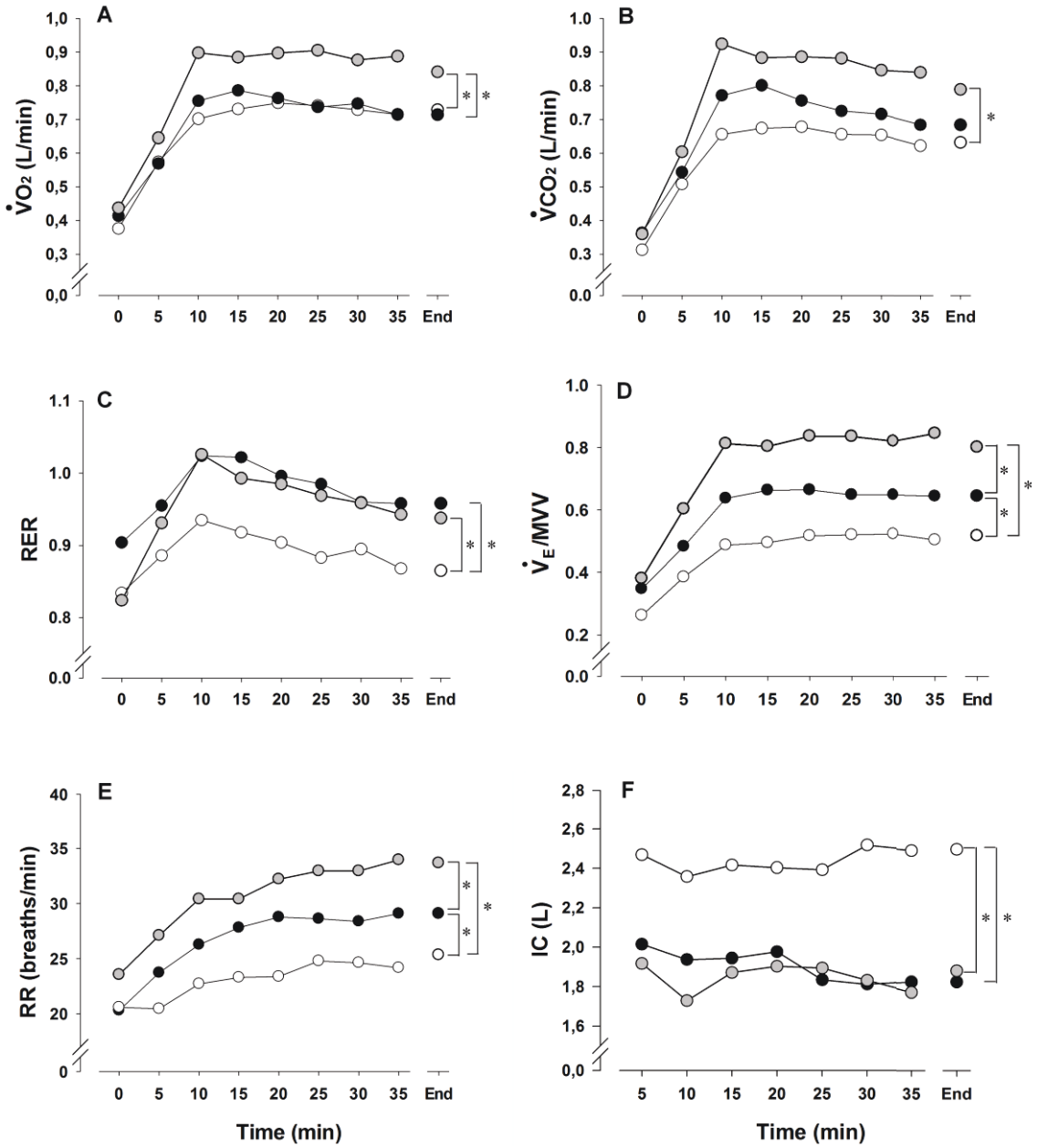


Figure 2.

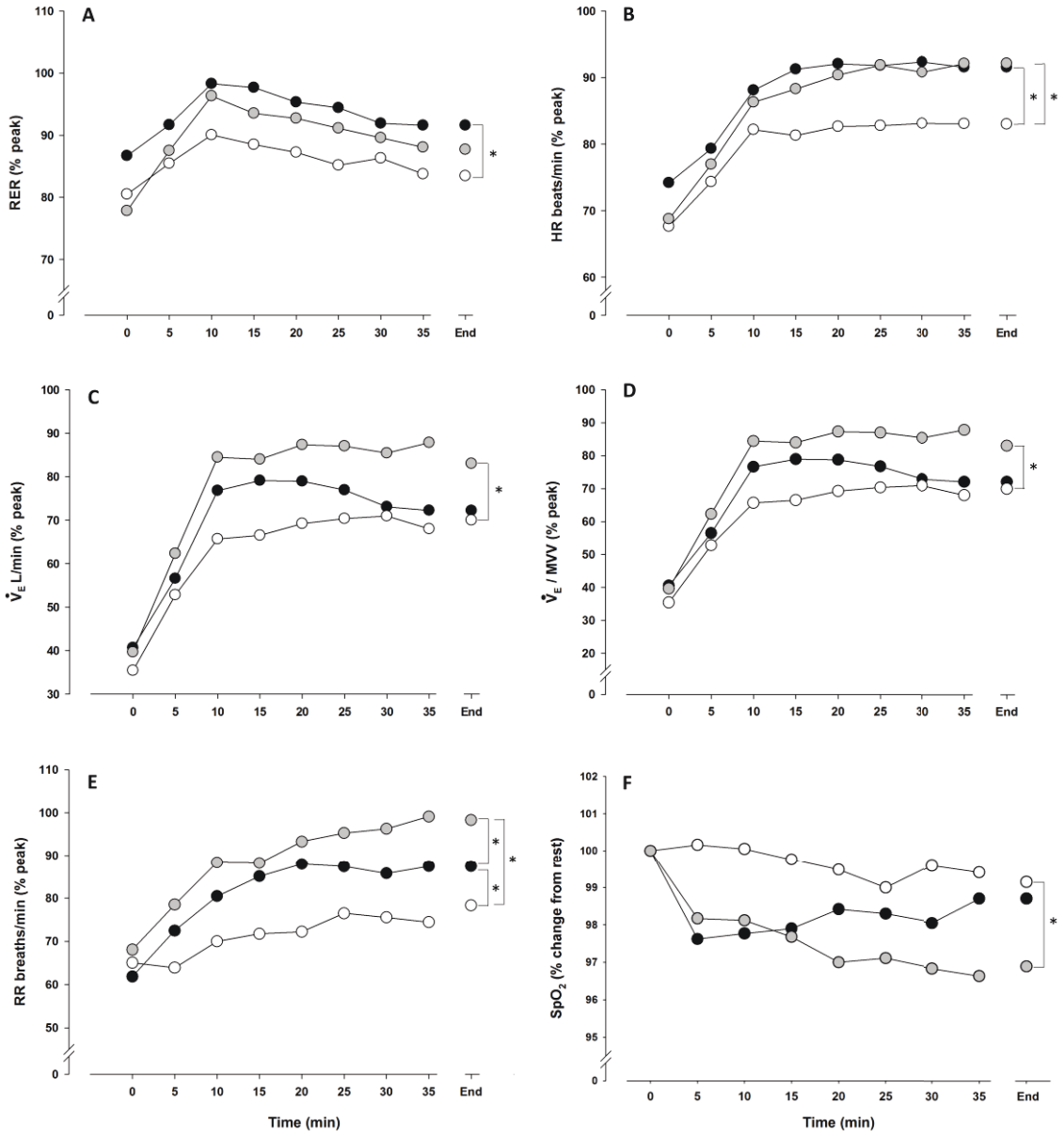

A
RER (% peak)
B
HR beats/min (% peak)
C
$\dot{V}_E$ L/min (% peak)
D
$\dot{V}_E$ / MVV (% peak)
E
RR breaths/min (% peak)
F
SpO_2 (% change from rest)
Time (min)
Time (min)
End

Figure 3.

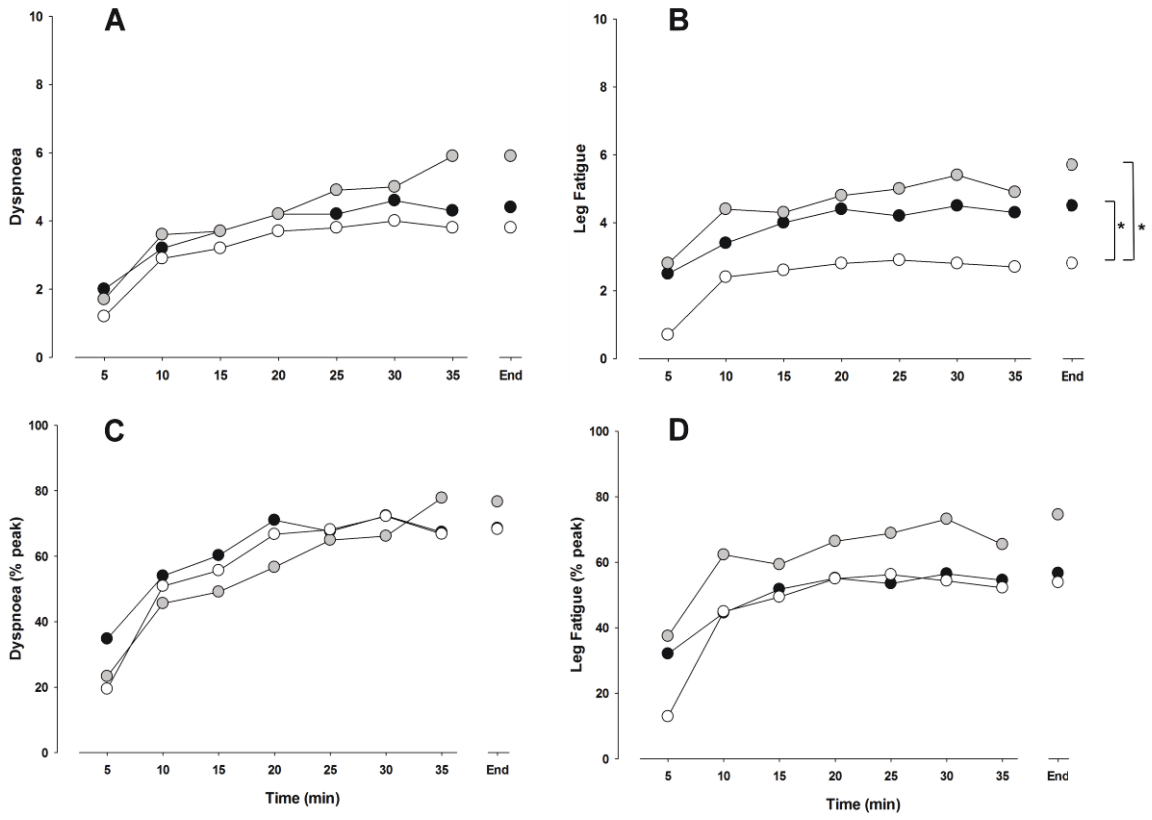

A
B
C
D
Dyspnoea
Leg Fatigue
Dyspnoea (% peak)
Leg Fatigue (% peak)
Time (min)
Time (min)
End
*
*

Figure 4.

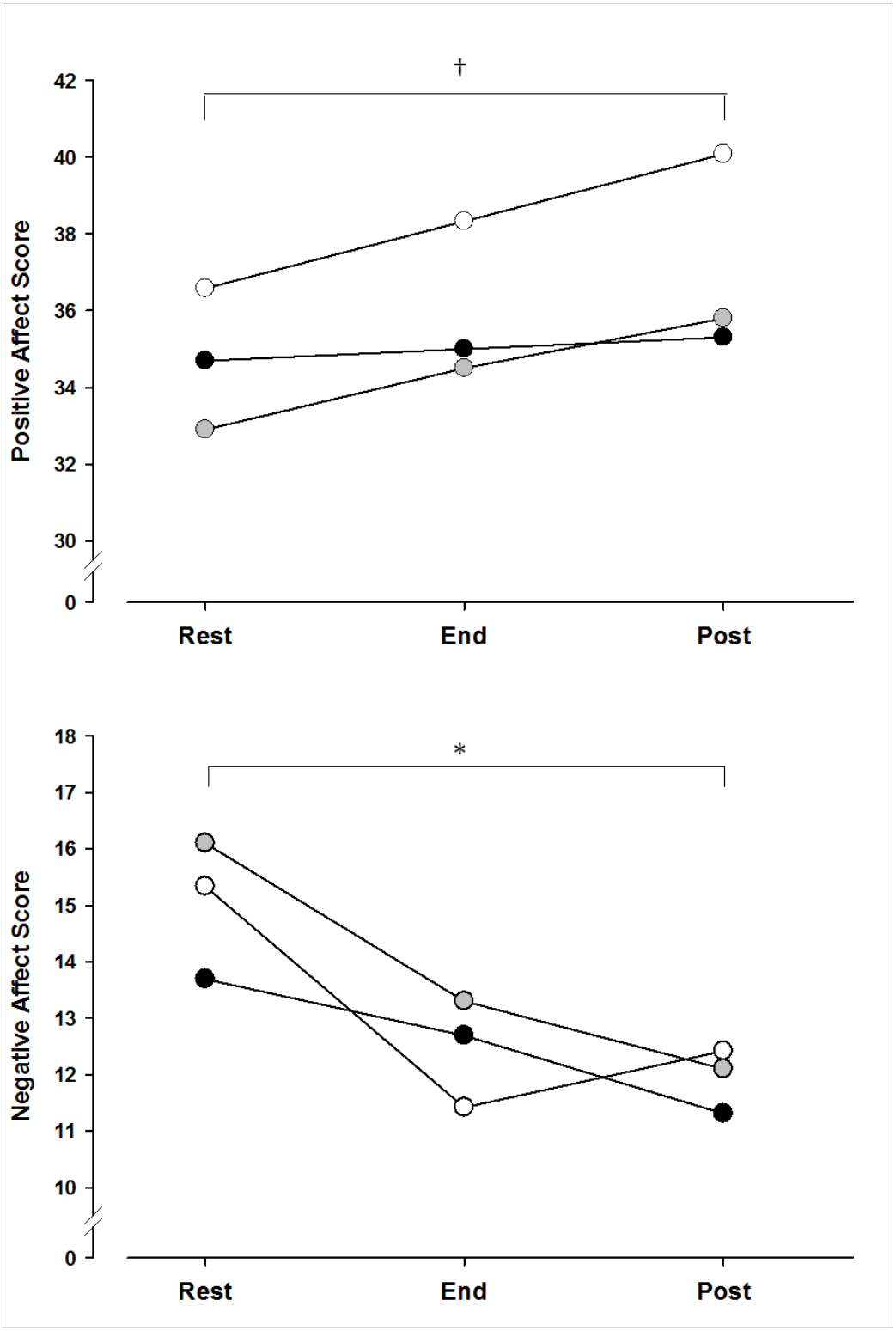

†
42
40
38
36
34
32
30
0
Positive Affect Score
Rest
End
Post
*
18
17
16
15
14
13
12
11
10
0
Negative Affect Score
Rest
End
Post

Figure 5.

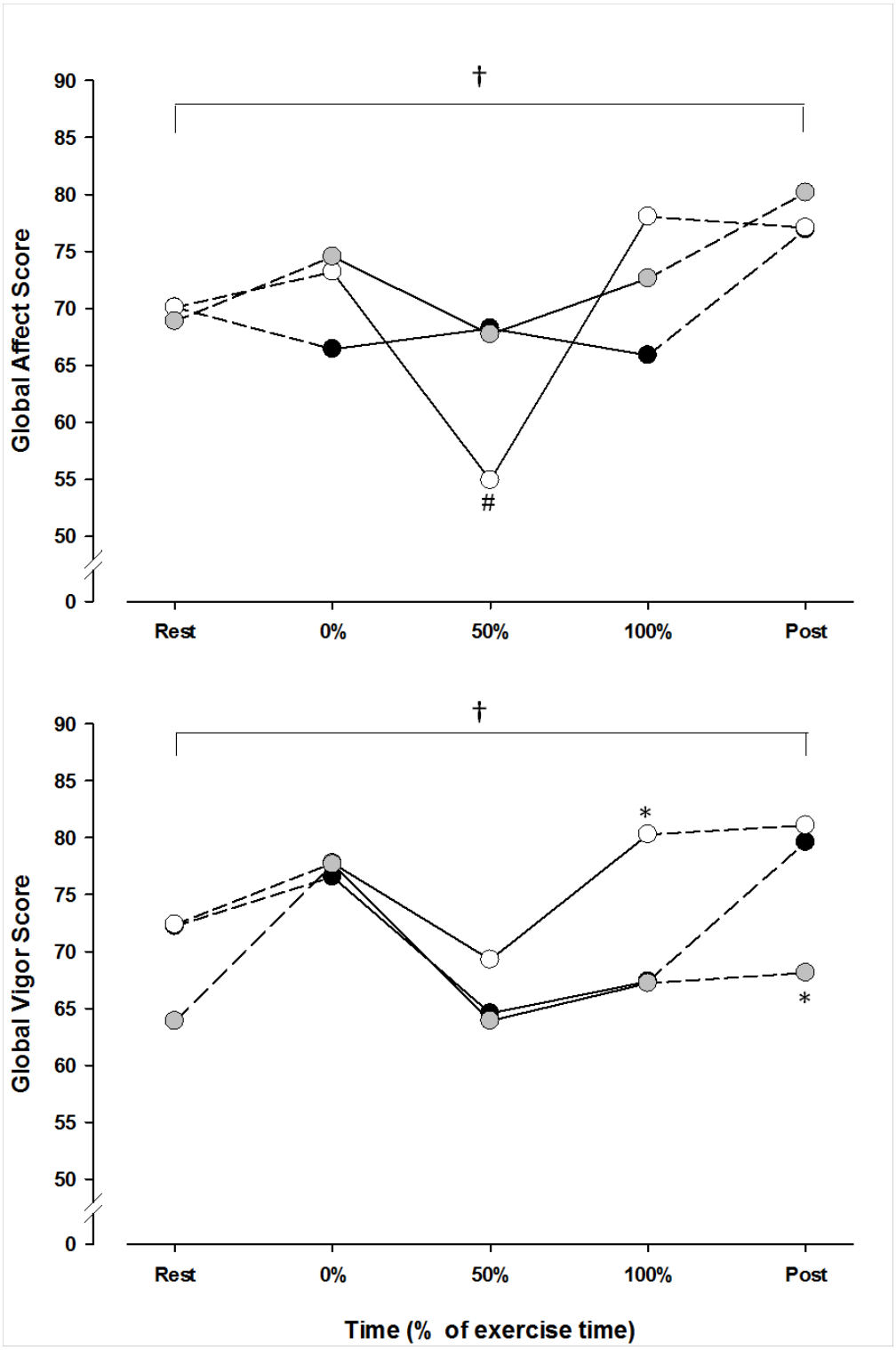

†
90
85
80
75
70
65
60
55
50
0
Global Affect Score
#
Rest
0%
50%
100%
Post
†
90
85
80
75
70
65
60
55
50
0
Global Vigor Score
*
*
Rest
0%
50%
100%
Post
Time (% of exercise time)

Figure 6.

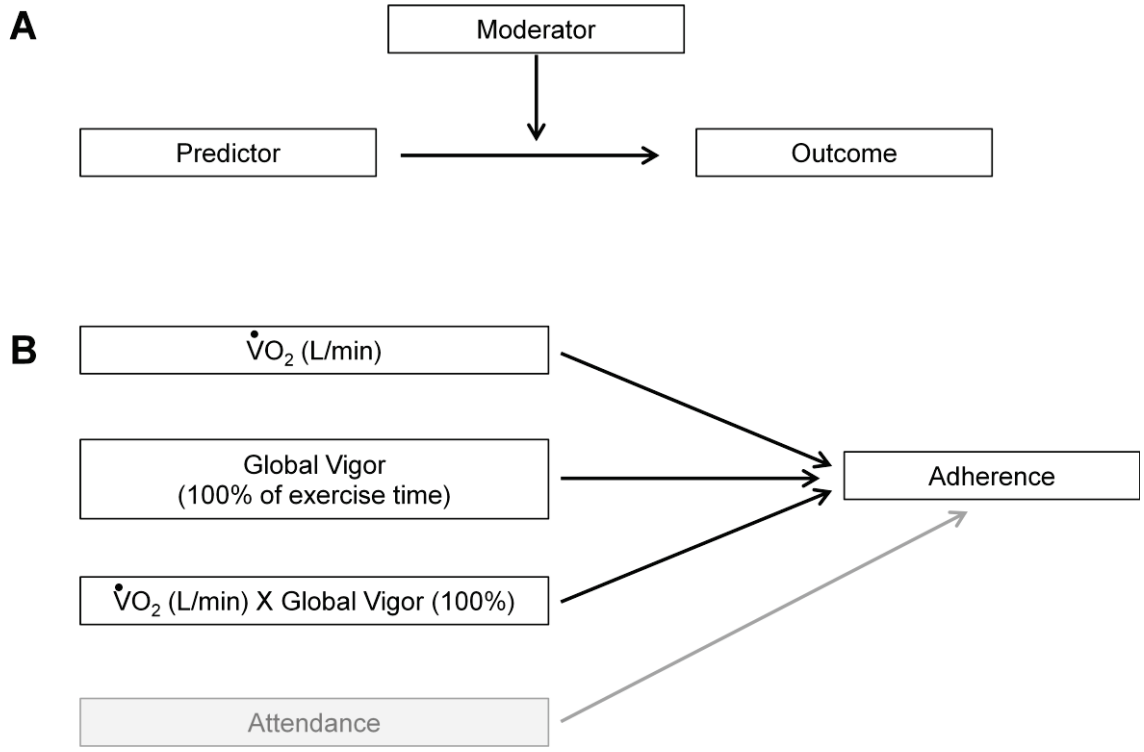
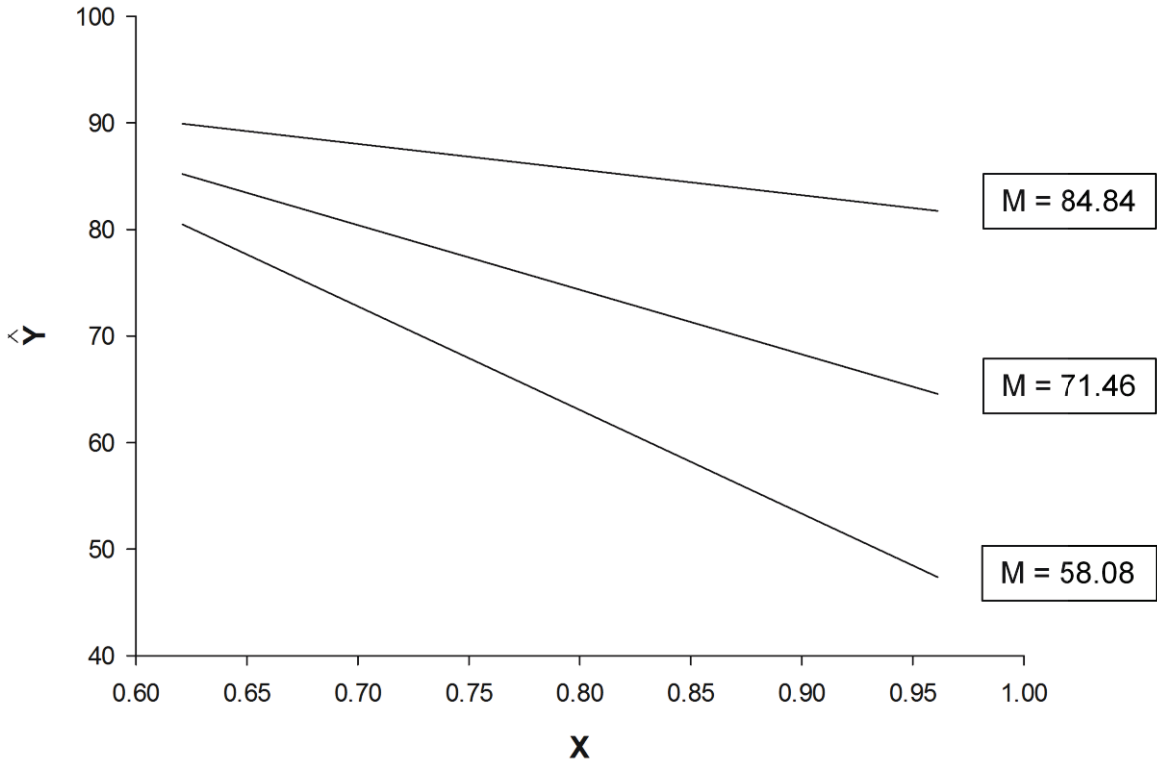

A
Moderator
Predictor
Outcome
B
$\dot{V}O_2$ (L/min)
Global Vigor
(100% of exercise time)
$\dot{V}O_2$ (L/min) X Global Vigor (100%)
Attendance
Adherence

Figure 7.


100
90
80
70
60
50
40
Y
0.60
0.65
0.70
0.75
0.80
0.85
0.90
0.95
1.00
X
M = 84.84
M = 71.46
M = 58.08

9. APPENDIX C: Manuscript - Mild Cognitive Impairment in Moderate to Severe Chronic Obstructive Pulmonary disease (Published)

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The authors report no conflict of interest.

Keywords: chronic obstructive pulmonary disease, mild cognitive impairment

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ABSTRACT

Introduction: Cognitive impairment is a frequent feature of chronic obstructive pulmonary disease (COPD). However, the proportion of COPD patients with mild cognitive impairment (MCI) is still unknown, and no screening test has been validated to date for detecting MCI in this population.

Objective: To determine the frequency and subtypes of MCI in COPD patients and to assess the validity of two cognitive screening tests, the Mini-Mental State Examination (MMSE), and the Montreal Cognitive Assessment (MoCA), in detecting MCI in COPD.

Methods: Forty-five moderate to severe COPD patients and 50 healthy controls underwent a comprehensive neuropsychological assessment using standard MCI criteria. Receiver operating characteristic curves were obtained to assess the validity of the MMSE and the MoCA to detect MCI in COPD patients.

Results: MCI was found in 36% of COPD patients compared to 12% of healthy subjects. COPD with MCI had mainly the nonamnestic MCI single domain subtype with predominant attention and executive dysfunctions. The optimal MoCA screening cut-off was 26 (≤25 indicates impairment, with 81% sensitivity, 72% specificity and 76% correctly diagnosed). No MMSE cut-off had acceptable validity.

Conclusions: A substantial proportion of COPD patients were found to have MCI, a known risk factor for dementia. Longitudinal follow-up on these patients is needed to determine the risk of developing more severe cognitive and functional impairments. Moreover, the MoCA is superior to the MMSE in detecting MCI in COPD patients.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a progressive disease characterized by partially irreversible chronic airflow limitation.[1-3] Typical onset is in middle adulthood (>55 years), and more than 14% of individuals over 65 years old are affected.[4] Cognitive impairment is one of the most frequent extrapulmonary manifestations in COPD,[5] and it has been associated with higher mortality and disability.[6,7] Assessing cognitive impairment in COPD patients should therefore provide relevant information on disease prognosis. Previous studies of cognitive performance in COPD versus healthy subjects found mostly poor performance on cognitive tests of attention, memory, and executive functions.[8] However, the proportion of COPD patients with clinically relevant cognitive impairments, based on standard criteria that can be readily applied in clinical and research settings, remains unknown.

Mild cognitive impairment (MCI) refers to significant cognitive decline without major functional impacts on daily living activities.[9,10] Individuals with MCI are of particular interest, because they are at higher risk for dementia,[10] including Alzheimer's disease (AD) and vascular dementia.[11] Longitudinal studies have shown that almost half the individuals that meet MCI criteria develop dementia within three years.[10,12] Accordingly, knowing the proportion of COPD patients with MCI would provide essential information about the frequency of clinically relevant cognitive decline in COPD patients, as well as objective long-term follow-up criteria and guidelines for selecting patients liable to benefit from therapeutic interventions.[10]

A comprehensive neuropsychological assessment is the most effective way to detect MCI. However, it is time-consuming and requires specialized training, and is often unavailable to COPD patients in clinical practice. Thus, efficient tools that can detect MCI in COPD patients are needed. The Mini-Mental State Examination (MMSE)[13] is the most commonly used test for screening cognitive impairments.[15] However, its sensitivity to MCI has been questioned,[14,15] particularly in individuals with executive dysfunctions. The Montreal Cognitive Assessment (MoCA) test is another five- to ten-minute cognitive screening tool designed to assist clinicians in detecting cognitive impairment.[16] The MoCA has been found superior to the MMSE in detecting MCI in various clinical populations.[15-18] However, the validity of these tests to detect MCI in COPD patients has never been established.

The aim of the present study was to determine the frequency and main subtype of MCI in moderate to severe COPD patients, and to assess the validity of the MMSE and the MoCA in detecting MCI in COPD patients.

PARTICIPANTS AND METHODS

Patient selection

In this prospective study, patients with COPD were referred by a pneumologist and recruited from the outpatient COPD clinic at the Hôpital du Sacré-Coeur de Montréal. The inclusion criteria were 1) clinically stable moderate to severe COPD according to the GOLD classification;[19] 2) post-bronchodilation forced expiratory volume in one second (FEV_1) less than 80% of the predicted normal value and FEV_1 to forced

vital capacity (FVC) ratio less than 0.7; 3) age 40 years or older; and 4) smoking history of at least 10 American pack-years (20 cigarettes per pack).

Exclusion criteria for COPD patients and controls were 1) exacerbation of respiratory symptoms in the past four weeks (change in dyspnoea and/or volume/color of sputum, need for antibiotic treatment, or need for hospitalization); 2) oxygen therapy; 3) presence of asthma, unstable coronary heart disease, uncontrolled diabetes or hypertension, left congestive heart failure, neoplasia, severe claudication, encephalitis, or epilepsy; 4) history of head injury or brain tumor; 5) major psychiatric condition according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)[20]; 6) dementia according to the DSM-IV-TR criteria and the neuropsychological assessment (i.e. at least two cognitive domains impaired, including verbal learning and memory). Cognitive deficits should be severe enough to exert a significant impact on daily living activities (i.e. medication management, meal preparation, finances, transportation, shopping and housekeeping), as assessed by a structured interview based on inhouse questionnaire; 7) age over 90 years; 8) language other than French or English; and 9) illiteracy.

Spirometry, lung volume assessment, and lung diffusion capacity for carbon monoxide (D_LCO) assessment were performed according to recommended procedures.[21] Results were compared to predicted normal values from the European Community for Coal and Steel and the European Respiratory Society.[22] Oxygen saturation (SaO2) was measured at rest.

Fifty healthy older adults were recruited from the general population through newspapers and by word of mouth. Most of the control subjects had participated in a previous study on cognition in Parkinson's disease.[23] Ethical approval was obtained from the hospital's ethics committee (IRB committee name and project approval number, Hôpital du Sacré-Cour de Montréal, 2008-01-107), and all participants gave their written informed consent according to the Helsinki Declaration.

Comorbidities

Vascular comorbidities (hypertension, hypotension, dyslipidemia, diabetes mellitus, carotid stenosis, history of coronary artery disease, transient cerebral ischemia, and cardiac arrhythmia) were computed in COPD patients to create a vascular burden score.[24] Comorbidities were assessed based on clinical records and information provided by participants or proxies during the medical interview. This index was not systematically assessed in all our control subjects. Therefore, we used a control group of 77 participants living in the same community as our sample,[24] and with equivalent age (70.04 ± 9.55), gender (19 men) and education (14.01 ± 3.41) for comparisons with our COPD patients.[24] The Epworth Sleepiness Scale (ESS) was administered to assess excessive daytime sleepiness.[25]

Neuropsychological tests and MCI criteria

COPD patients and controls underwent comprehensive neuropsychological testing by a neuropsychologist according to standard procedures.[26] Table 1 presents the cognitive domains, tests, variables, and normative data used. COPD patients began with

the MoCA[16] followed for all the participants by the MMSE[13] and the other neuropsychological tests in the same two–hour session. Questions on orientation (date, month, year, day of the week, place, and city) were asked only once, on the MoCA, and these orientation scores were added to the scores on the MMSE. Following standard procedure,[16,27] one point was added to the MoCA score for patients with 12 years of education or less.

All the following criteria should be met for an MCI diagnosis:[9,28,29] (1) a subjective complaint of cognitive change by the patient or informant on a structured interview or the Cognitive Failures Questionnaire (CFQ)[30] (based on a total score >24, or, on at least one item, the response 3: quite often or 4: very often); (2) objective evidence of cognitive decline defined as at least two scores in a same cognitive domain ≥1.5 standard deviations below the standardized mean, adjusted for age and education (Table 1); (3) preserved daily living activities (see exclusion criteria number 6 above); and (4) cognitive deficits not better explained by other medical or psychiatric disorders or medication use.

MCI were classified into four subtypes: amnestic MCI single domain (isolated learning and memory deficit), nonamnestic MCI single domain (either attention and executive functions or visuospatial impairment), amnestic MCI multiple domain (learning and memory deficit plus impairment in another cognitive domain), and nonamnestic MCI multiple domain (attention and executive dysfunction plus visuospatial impairment).[9]

Insert Table 1 about here

Statistical Analysis

Student's t-tests were performed to assess group differences in continuous data. Categorical variables were compared using Pearson Chi-square tests. A receiver operator characteristic (ROC) curve with area under the curve (AUC) (95% CI) was used to assess the sensitivity, specificity, negative predictive values (NPV), positive predictive values (PPV), and percentage of correctly diagnosed patients using total scores on the MoCA and the MMSE to detect MCI in COPD patients. Three cut-offs were proposed for each screening test: 1) the **optimal screening value,** or the lowest value with >80% sensitivity and NPV; 2) the **optimal diagnostic value,** or the highest value with >80% specificity and PPV; and 3) the **maximum accuracy value,** calculated by the Youden Index [y = sensitivity + specificity - 1].[45] Statistical significance was set at $p<0.05$.

RESULTS

Of the 53 COPD patients invited to participate in the study, eight were excluded (five refused, one for concomitant schizophrenia, one for alcoholism, and one for native language other than French or English), for a final sample of 45 COPD patients (see Table 2 for sociodemographic and clinical characteristics). No significant differences were found between COPD patients and controls for age, gender, educational level, or excessive daytime sleepiness (Epworth score). COPD patients had more vascular comorbidities and more cognitive complaints than controls (average CFQ score and proportion of patients with a total score >24).

Insert Table 2 about here

Mild cognitive impairment

MCI was found in 36% (16/45) of COPD patients compared to 12% (6/50) of control subjects [χ^2 (1) = 7.39, p = 0.007] (Fig 1). The main MCI subtype in COPD was nonamnestic MCI single domain, with predominant attention and executive dysfunctions. COPD with MCI had a lower education level than COPD without MCI and controls (Table 2). Processing speed slowing was found in three COPD patients (two with MCI) and one control subjects (without MCI). No difference was found between COPD patients with and without MCI in age, gender, disease severity, pulmonary capacity [a tendency was found for D_LCO (ml/mmHg/min)], antidepressant or antianxiety medication intake, vascular comorbidities, or excessive daytime sleepiness.

Insert Figure 1 about here

Screening tests for MCI in COPD

MoCA

The mean MoCA score ± SD was 25.64 ± 2.89 (range 20–30). The ROC curve analysis for MoCA showed an area under the curve of 0.82 (CI 95%: 0.68–0.96). The optimal screening value was 26 (≤25 indicates impairment; 81% sensitivity; 72%

specificity; 76% correctly diagnosed), maximum accuracy was 25 (≤24 indicates impairment; 75% sensitivity; 79% specificity; 78% correctly diagnosed), and the optimal diagnostic value was 23 (≤22 indicates impairment; 44% sensitivity; 93% specificity; 76% correctly diagnosed) (Table 3).

MMSE

The mean MMSE score ± SD was 28.31 ± 1.58 (range 22–30). The MMSE had an area under the curve of 0.63 (CI 95%: 0.45–0.81). The optimal screening value was 30 (≤29 indicates impairment; 88% sensitivity; 28% specificity; 49% correctly diagnosed), maximum accuracy was 27 (≤26 indicates impairment; 31% sensitivity; 97% specificity; 73% correctly diagnosed), and the optimal diagnostic value was 27 (≤26 indicates impairment; 31% sensitivity; 97% specificity; 73% correctly diagnosed) (Table 3).

Insert Table 3 about here

DISCUSSION

The main finding of this preliminary study was that patients with moderate to severe COPD are at high risk for MCI, with an estimated 36% frequency. This is significantly higher than the proportion of MCI found in healthy controls matched for age, gender, education, and severity of excessive daytime sleepiness. Moreover, we found convincing evidence that the MoCA is a more reliable screening test than the MMSE in detecting MCI in COPD patients.

MCI in COPD

MCI is a syndrome defined as the presence of significant cognitive decline that does not notably interfere with social or occupational functioning.[9,10] The high frequency of MCI found in our COPD population is in line with previous studies that reported poor cognitive performance in COPD patients.[8] However, only a few studies have assessed the proportion of COPD patients with cognitive impairment, and to our knowledge, none of them used standard MCI criteria that can be readily applied in clinical and research settings. Cognitive impairment in COPD has been associated with higher mortality and disability.[6,7] Therefore, detection and assessment of MCI in COPD is needed to provide patients with appropriate follow-up and management. All types of dementia, including AD, vascular dementia, mixed dementias, dementia with Lewy bodies, Parkinson's disease dementia, or fronto-temporal dementia may have a prodomal phase.[46] Considering that MCI is a risk factor for dementia,[9-12] it is important to identify individuals with MCI in aged clinical populations, such as COPD patients. In fact, approximately half of MCI patients will progress to dementia within three to five years.[10,12] However, increasing evidence indicates that not all MCI patients will eventually develop dementia; some remain stable over time while others return to normal.[10,47] It remains unknown whether COPD patients with MCI are in a prodromal phase of dementia, or if they account for some of the MCI patients who stay stable over time or return to normal. Recent evidence indicates that cognitive impairment worsens over time in severe COPD patients,[48] suggesting that COPD patients with MCI may be at higher risk for dementia, such as AD, vascular dementia, or mixed dementias. However, future studies using neuroimaging or biomarkers are needed to explore this issue.

We found that the main MCI subtype in COPD was nonamnestic MCI single domain, with predominant attention and executive dysfunctions. The second most commonly impaired cognitive domain was verbal learning and memory. Attention, memory, and executive functions are often reported as the most commonly impaired cognitive domains in COPD patients.[8] Neuroimaging studies have reported reduced cerebral blood flow in the frontal and subcortical areas in COPD, which may explain the attention/executive dysfunctions reported.[5,8,49]

The underlying mechanisms of cognitive impairments in COPD remain controversial and poorly understood.[8] Hypoxaemia or vascular comorbidities have been proposed as a possible cause of brain alterations in COPD patients.[8] In our study, COPD patients had more vascular comorbidities than controls, which is reported by other studies.[8,50] However, the respiratory measures and vascular comorbidities were similar between COPD with MCI and COPD without MCI patients. This suggest that these factors alone are unlikely to account for MCI in COPD patients. Similar conclusions had previously been proposed.[8] However, our results must be replicated in a larger sample size and subjected to other types of statistical analysis.

Education is the only significant difference between COPD-MCI compared to COPD-NoMCI patients and controls. Our results are in line with other studies showing that low education is a well recognized risk factor for MCI.[51,52] In our study, we tried to minimize the effect of these variables using normative data adjusted for age and education. Moreover, controls and COPD patients were well matched for age and

education. Therefore, these factors cannot account for the higher frequency of MCI found in COPD than in controls. Some may argue that this may reflect a difference in pre morbid status rather than cognitive decline. We cannot exclude that possibility, but none of our COPD patients was illiterate and all had completed at least primary school, which suggests that all COPD patients had adequate pre morbid abilities. On the other hand, education and pre morbid status are two major determinants of cognitive reserve.[53,54] This concept refers to the individual differences in how people process tasks allow some people to cope better than others with brain damage.[53] Interestingly, both COPD with MCI and COPD without MCI groups had an higher level of subjective complaint of cognitive change, suggesting that only a subgroup of COPD patients were able to perform in the normal range on cognitive tasks. The other COPD patients, with less education and than less cognitive reserve, were unable to compensate and were at higher risk to fulfill MCI criteria. We are therefore unable to determine the specific role played by education or premorbid status in the frequency of MCI in COPD, because education, premorbid status, cognitive reserve, and MCI were strongly interrelated. Only a longitudinal follow-up will allow a better understanding of MCI progression in COPD patients.

Cognitive screening tests in COPD

Several screening tests have been developed to help clinicians detect cognitive impairments in elderly populations.[15] To our knowledge, none has been validated for detecting MCI in COPD patients. Our study assessed the validity of the MMSE and the MoCA in detecting MCI in COPD patients based on optimal screening, diagnostic, and maximum accuracy values.

For the MoCA, an optimal cut-off of 25 (≤24 indicates impairment) was identified as the maximum accuracy value, with good sensitivity (75%) and specificity (79%) and 78% correct classification. However, for screening purposes, a normality cut-off of 26 (≤25 indicates impairment) should be used, increasing sensitivity to 81% but reducing specificity to 73%, with 88% negative predictivity and 76% correct classification. Accordingly, a neuropsychological assessment should be performed in COPD patients without cognitive complaints who score <26 on the MoCA to better characterize their cognitive profile and to exclude the presence of MCI. On the other hand, if the MoCA is used as a diagnostic tool for MCI in COPD patients, a normality cut-off of 23 (≤22 indicates impairment) is suggested, increasing specificity to 93% at the cost of lower sensitivity (44%) and correct classification (76%). However, a substantial proportion of COPD patients with MCI would remain undetected, and a comprehensive neuropsychological investigation would be required to confirm the presence of MCI in patients with cognitive complaints who score >22 on the MoCA.

For the MMSE, no acceptable cut-off for detecting MCI in COPD was identified based on the optimal screening value. The suggested optimal screening cut-off of 30 (≤29 indicates impairment) shows very good sensitivity at 88%, but very poor specificity at 28%, and only 49% correct classification. The optimal maximum accuracy and diagnostic cut-off was 27 (≤26 indicates impairment), which allowed excellent specificity (97%) but poor sensitivity (31%), with 73% correct classification. Although the MMSE is the most commonly used screening test to detect cognitive impairment in the elderly, its validity for detecting MCI and more severe cognitive deficits in COPD patients has been questioned.[15,55] The MMSE is insensitive to attention and executive dysfunctions, the

main cognitive deficits reported in COPD. Previous studies have also suggested that the MoCA is superior to the MMSE in detecting MCI in clinical populations with predominant impaired attention and executive functions.[18,19] Hence, compared to the MMSE, the current study shows that the MoCA is an appropriate and validated brief screening test for detecting MCI in COPD patients.

Some limitations of this study should be noted. Although our neuropsychological battery was relatively extensive, working memory was not tested using more complex cognitive tasks than the Digit Span. Moreover, we did not include in our study patients with mild or very severe COPD. The latter may have significant cognitive impairment while mild COPD patients may present attention and executive dysfunctions that could interfere with the compliance of their treatment. Our results need to be replicated in a larger sample size that includes patients with a wider severity range of COPD. The criteria for selection of the controls (i.e. through newspapers and by word of mouth) might have created a selection bias. However, the frequency of MCI observed in our healthy control group (12%) is representative of what it is usually reported in population-based studies (3 to 19%).[10]

In conclusion, a substantial proportion of patients with moderate to severe COPD have MCI, a risk factor for dementia. Longitudinal follow-up is therefore needed on these patients to determine the risk of developing more severe cognitive and functional impairments. Furthermore, the MoCA (available free at http://www.mocatest.org/) is valid for detecting MCI in COPD patients.

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Author Roles: S. Villeneuve participated in the data acquisition, analysis, and interpretation, wrote the first draft of the manuscript, and revised it following critical reviews by the coauthors. V. Pepin participated in the study design, data acquisition and interpretation, study coordination, and fundraising, and critically reviewed the manuscript. Shady Rahayel participated in the data acquisition and analysis and critically reviewed the manuscript. J.-A. Bertrand participated in the data acquisition and interpretation and graphic design and critically reviewed the manuscript. M. Delorimier, A. Rizk, C. Desjardins, and O. Monchi participated in the data acquisition and critically reviewed the manuscript. S. Parenteau and F. Beaucage referred COPD patients, participated in the data acquisition, and critically reviewed the manuscript. S. Joncas participated in the study design and critically reviewed the manuscript. J.-F. Gagnon participated in the study design, data acquisition and interpretation, study coordination and supervision, and fundraising, and critically reviewed the manuscript.

Table 1. Neuropsychological testing

Cognitive Domains and Neuropsychological Tests	Variables and normative data	Criteria for Defining Impairment
Attention and executive functions		2/5 variables abnormal
Digit Span (forward and backward)[31]	Scaled score[31]	—
TMT, part B[32]	Time (sec)[33]	—
SCWT (D-KEFS)[a,34] (modified version)[b,35]	Part IV – part II (time, sec) or part IV (number of errors)[a,34] Part III – part I (time, sec) or part III - part I (number of errors)[b,23]	—
Semantic verbal fluency (animals and boy's names)[a,34] (animals, fruits, & vegetables)[b]	Number of words (1 min)[34,36]	—
Letter verbal fluency (P, F, and L)[34,37]	Number of words (1 min)[34,38]	—
Verbal learning and memory		2/5 variables abnormal
RAVLT (15 words)[39]	Sum of trials 1 to 5, List B, immediate recall, delayed recall (20 min), recognition[40]	—
Visuospatial abilities		2/3 variables abnormal
Copy of the Rey-O figure[41]	Score/36 (40–68 years old,[42] ≥69 years old[43])	—
Block Design[31]	Scaled score[31]	—

Bells Test[44]	Number of omissions[44]	—
Processing speed[c]		2/3 variables abnormal
TMT, part A[32]	Time (sec)[33]	—
Coding[31]	Scaled score[31]	—
SCWT (D-KEFS)[a,34] (modified version)[b,35]	Part I (time, sec)[a,34] Part I (time, sec)[b,23]	—

TMT = Trail Making Test; SCWT = Stroop Color Word Test; D-KEFS = Delis-Kaplan Executive Function System; RAVLT = Rey Auditory-Verbal Learning Test

[a]Included in the assessment of COPD patients.

[b]Included in the assessment of controls.

[c]Not included as mild cognitive impairment subtype.

Table 2. Demographic and clinical characteristics

Characteristics	COPD patients			Control subjects	*p*	*p*
	Total (n = 45)	MCI (n = 16)	NoMCI (n = 29)	Total (n = 50)	All COPD vs. Control	COPD-MCI vs. NoMCI
Demographic						
Age (years)	68.42 ± 8.72	71.25 ± 7.52	66.86 ± 9.07	67.44 ± 8.77	0.59	0.11
Gender (M/F)	16/29	5/11	11/18	20/30	0.58	0.65
Education (years)	12.27 ± 4.05	10.06 ± 3.21	13.48 ± 4.00	13.14 ± 2.92	0.23	**0.005**[¥]
Cognitive complaint						
CFQ total score	31.75 ± 11.25	33.08 ± 11.00	31.08 ± 11.55	23.84 ± 11.67	**0.006**	0.62
CFQ score >24 (%)	72	83	67	33	**0.004**	0.29
Daytime sleepiness						
Epworth total score	6.97 ± 3.50	8.42 ± 3.09	6.28 ± 3.53	6.29 ± 4.19	0.45	0.62
Medications						
Antidepressants use (No.)	10	3	7	-	-	0.68
Antianxiety use (No.)	10	4	6	-	-	0.95
Vascular comorbidities						
Vascular burden index	1.29 ± 1.12	1.56 ± 1.26	1.14 ± 1.56	0.90 ± 1.01[†]	**0.05**	0.23

COPD clinical status				-	-	
Disease severity (moderate/severe)	25/20	10/6	15/14	-	-	0.49
FEV_1 (L)	1.34 ± 0.42	1.38 ± 0.38	1.32 ± 0.45	-	-	0.69
FEV_1 (predicted %)	54.51 ± 14.45	58.44 ± 12.03	52.34 ± 15.39	-	-	0.18
FVC (L)	2.78 ± 0.71	2.80 ± 0.70	2.77 ± 0.72	-	-	0.89
FVC (predicted %)	91.96 ± 17.92	97.88 ± 21.45	88.69 ± 15.06	-	-	0.10
FEV_1/FVC	0.48 ± 0.10	0.50 ± 0.09	0.48 ± 0.10	-	-	0.53
D_LCO (ml/mmHg/min)	22.18 ± 2.88	20.76 ± 2.33	22.82 ± 2.91	-	**-**	**0.06**
D_LCO (predicted %)	51.74 ± 12.36	47.9 ± 11.42	53.57 ± 12.64	-	-	0.24
SaO2	95.49 ± 1.52	95.27 ± 1.56	95.63 ± 1.50	-	-	0.48

Data are shown as mean ± S.D.

CFQ = Cognitive Failures Questionnaire; COPD = chronic obstructive pulmonary disease; D_LCO = single-breath carbon monoxide diffusion capacity; FEV_1= forced expiratory volume in one second; FVC = forced vital capacity; MCI = COPD patients with mild cognitive impairment; NoMCI = COPD patients without mild cognitive impairment; SaO2 = oxygen saturation; [¥]Also significant between COPD with MCI and controls; [†]From an equivalent control group (see participants and methods section).[24]

Table 3: Validity of the Montreal Cognitive Assessment and the Mini-Mental State Examination in detecting mild cognitive impairment in chronic obstructive pulmonary disease

MoCA								
Cut-off	30/29	29/28	28/27	27/26	**26/25**[a]	**25/24**[c]	24/23	**23/22**[b]
Sensitivity	94	94	94	88	81	75	56	44
Specificity	14	34	41	55	72	79	90	93
PPV	38	44	47	52	62	67	75	78
NPV	80	91	92	89	88	85	79	75
% Correctly diagnosed	42	56	60	67	76	78	78	76
AUC (95% CI) 0.82 (0.68–0.96)								
MMSE								
Cut-off	**30/29**[a]	29/28	28/27	**27/26**[b, c]	26/25	25/24	24/23	23/22
Sensitivity	88	50	38	31	6	6	6	6
Specificity	28	55	86	97	100	100	100	100
PPV	40	38	60	83	100	100	100	100
NPV	80	67	71	72	66	66	66	66
% Correctly diagnosed	49	53	69	73	67	67	67	67
AUC (95% CI) 0.63 (0.45–0.81)								

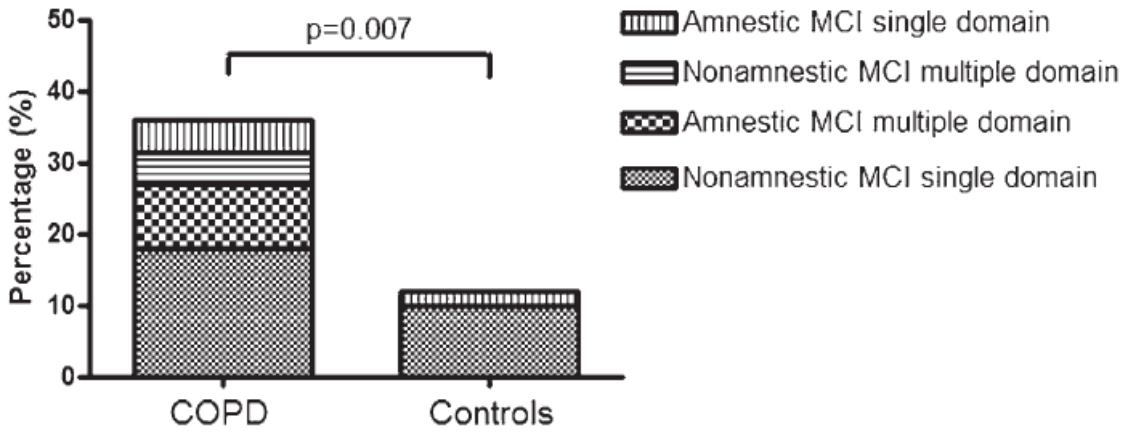
MoCA = Montreal Cognitive Assessment; PPV = positive predictive value; NPV = negative predictive value; AUC = area under the curve; CI = confidence interval; MMSE = Mini-Mental State Examination.

[a]**Optimal screening value** (Lowest value with sensitivity and NPV at ~ 80%).
[b]**Optimal diagnostic value** (Highest value with specificity and PPV at ~ 80%).
[c]**Maximum accuracy value** according to the Youden Index.

Figure legend

Fig 1. Percentage of mild cognitive impairment (MCI) in chronic obstructive pulmonary disease (COPD) patients and control subjects. Eight of the COPD patients with MCI had nonamnestic MCI single domain (7 with attention and executive dysfunctions and 1 with visuospatial impairment), 4 had amnestic MCI multiple domain (3 with memory and attention and executive dysfunctions and 1 with all domains impaired), 2 had nonamnestic MCI multiple domain, and 2 had amnestic MCI single domain. In the control group, 5 subjects had nonamnestic MCI single domain (all associated with impaired attention and executive functions) and 1 had amnestic MCI single domain.

Fig 1.



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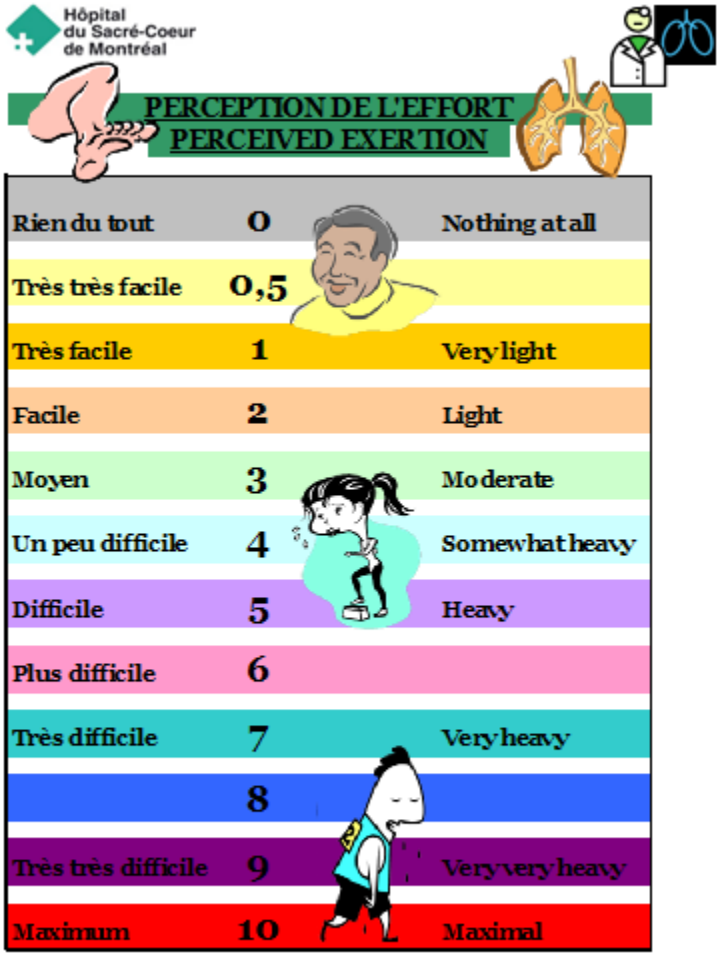
10. APPENDIX D: Modified 10-Point Borg Scale



Adapté de:
Borg, G.A.V. Psycho-physical basis of perceived exertion. Med. Science in Sport Exercise. 1982; vol 14(5):377-81

11. APPENDIX E : Positive and Negative Affect Schedule (PANAS)

Directions

This scale consists of a number of words that describe the different feelings and emotions. Read each item and then circle the appropriate answer next to that word.

	Very slightly or not at all	A little	Moderately	Quite a bit	Extremely
1. Interested	1	2	3	4	5
2. Distressed	1	2	3	4	5
3. Excited	1	2	3	4	5
4. Upset	1	2	3	4	5
5. Strong	1	2	3	4	5
6. Guilty	1	2	3	4	5
7. Scared	1	2	3	4	5
8. Hostile	1	2	3	4	5
9. Enthousiastic	1	2	3	4	5
10. Proud	1	2	3	4	5
11. Irritable	1	2	3	4	5
12. Alert	1	2	3	4	5
Indicate to what extent you	1	2	3	4	5
14. Inspired	1	2	3	4	5
15. Nervous	1	2	3	4	5
16. Determined	1	2	3	4	5
17. Attentive	1	2	3	4	5
18. Jittery	1	2	3	4	5
19. Active	1	2	3	4	5
20. Afraid	1	2	3	4	5

12. APPENDIX F: Global Vigor and Affect (GVA) Instrument

Name _____ Day _____ Date ___/___/___ Time _____

How alert do you feel?
Very little _____ very much

How sad do you feel?
Very little _____ very much

How tense do you feel?
Very little _____ very much

How much of an effort is it to do anything?
Very little _____ very much

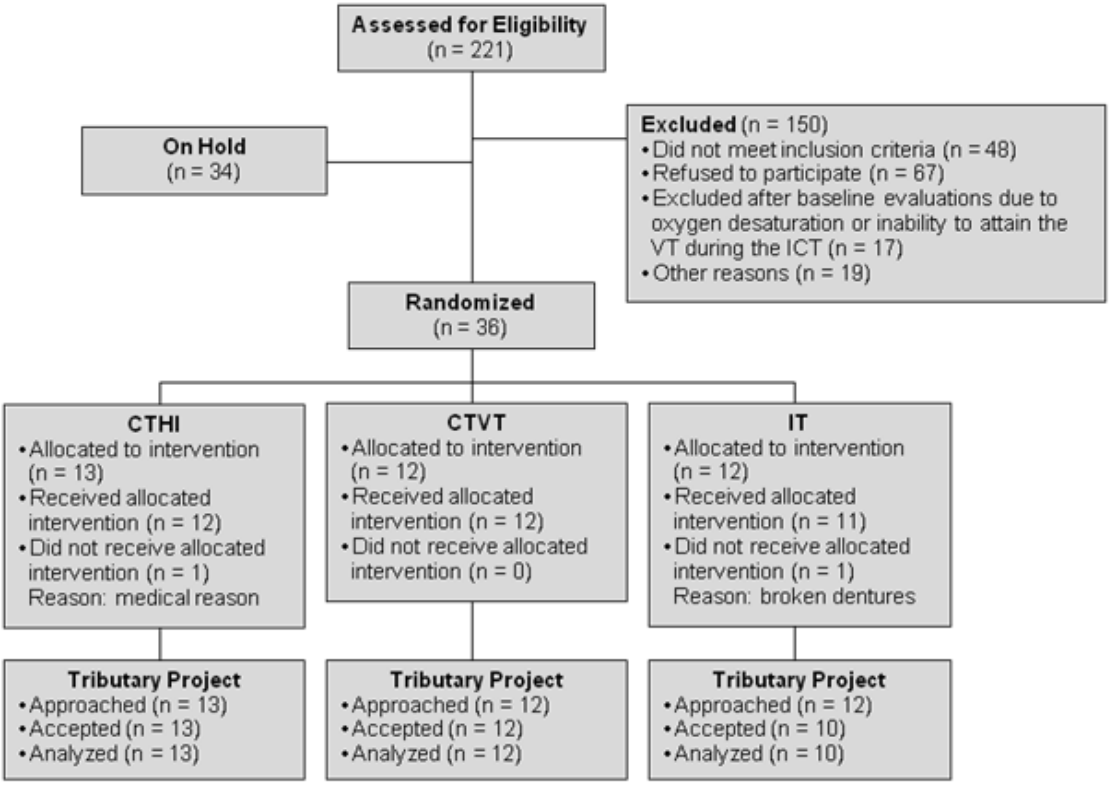
How happy do you feel?
Very little _____ very much

How weary do you feel?
Very little _____ very much

How calm do you feel?
Very little _____ very much

How sleepy do you feel?
Very little _____ very much

13. APPENDIX G: Flow of Participants



14. APPENDIX H: Talent Release Form (JoVE Video)

Talent Name: _____ Project Title: _____

I hereby consent for value received and without further consideration or compensation to the use (full or in part) of all videotapes taken of me and/or recordings made of my voice and/or written extraction, in whole or in part, of such recordings or musical performance for the purposes of illustration, broadcast, or distribution in any manner.

at _____ on _____

(Recording Location) (Date)

by _____ for _____

(Producer) (Producing Organization)

Talent's signature_____

Address _____ City _____

State _____ Zip code _____

Date: ____/____/____

_____

If the subject is a minor under the laws of the state where modeling, acting, or performing is done:

Legal guardian _____ _____

(sign/print name)

Address _____ City _____

State _____ Zip Code _____

Date: ____/____/____

15. APPENDIX I: Post-Hoc Power Calculations

Repeated-measures general linear models: (known: N = 35, α = 0.05)

Power calculation software used:

Power Analysis and Sample Size (PASS) (version 11.0)

Kaysville, Utah, U.S.A.

Reference: Hintze J., 2011

Equations Used:

σ_m = square root of $\frac{df \times MSE \text{ (Mean Square Effect)}}{N}$

$\sigma = \sqrt{MSE}$ (Mean Square Error)

Effect size = $f = \frac{\sigma_m}{\sigma}$

df for time effect = k – 1, where k = # of groups

df for time x intervention interaction = (k – 1) (l – 1), where k = # of groups, l = # of repeated measures

Sample Post-Hoc Power Calculation for Time Effect Observed for Positive Affect Using PANAS:

df = k – 1 = 3 – 1 = 2
MSE = 47.3 (taken from SAS output)
N = 35
α = 0.05

σ_m = square root of $\frac{df \times MSE}{N}$

= square root of $\frac{2 \times 47.3}{35}$

= 1.64

$\sigma = \sqrt{MSE}$
$= \sqrt{11.02}$
$= 3.32$

Effect size = $f = \frac{\sigma_m}{\sigma}$
$= \frac{1.64}{3.32}$
$= 0.49$

Entered σ_m, σ, N, and α into software to obtain power.

Post-Hoc Power Calculations:

PANAS - PA → Time Effect → power = 0.95

NA → Time Effect → power = 0.99

GVA – GA → Time x Intervention Interaction → power = 0.93

GV → Time x Intervention Interaction → power = 0.99

Partial Correlations: (known: N = 34, $\alpha = 0.05$)

- Correlation between Workload (W) and Adherence → r = 0.43 → power = 0.74
- Correlation between VO_2 (L/min) and Adherence → r = 0.47 → power = 0.82
- Correlation between V_E (L/min) and Adherence → r = 0.46 → power = 0.88
- Correlation between Global Vigor at end-exercise and Adherence → r = 0.42 → power = 0.81
- Correlation between VO_2 (L/min) and V_E (L/min) → r = 0.77 → power = 0.99
- Correlation between VO_2 (L/min) and Workload (W) → r = 0.83 → power = 0.99