Master's thesis

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Effect of Short-Term Sprint Interval Training on Cardiovascular Function in Patients with Chronic Obstructive Pulmonary Disease

Master's thesis in Exercise Physiology
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Abstract

Background: Interval training is well tolerated and recommended to enhance exercise capacity and alleviate respiratory symptoms during pulmonary rehabilitation in all stages of chronic obstructive pulmonary disease (COPD). Sprint interval training (SIT) is a new modality of interval training which has been found to improve both aerobic and anaerobic performance in healthy and sedentary populations. Cardiovascular disorders alongside with exertional dyspnea are major limitations of exercise tolerance in COPD. Therefore, SIT may favor cardiovascular adaptation and reduce respiratory symptoms irritations during high-intensity training with COPD patients.

Aim: To investigate the effect of short-term SIT on cardiovascular function and aerobic performance in patients with COPD and healthy elderly individuals.

Methods: Two groups of COPD patients (n = 10, age = 70.7 ± 7.7 years) and matched elderly subjects (n = 9, age = 65.4 ± 3.6 years) were recruited to perform SIT. Stroke volume (SV) and cardiac output (CO) were assessed using impedance cardiograph during rest, standard workload and maximal exercise test at baseline and after the training intervention. Exercise time to exhaustion was assessed at baseline and after SIT. The anaerobic performance was analyzed from changes in peak power during SIT from the second to the last training session. SIT program consisted of repeated 4 sprint bouts (20 sec) with all-out effort interspersed with 3-5 minutes recovery time for 3 weeks.

Results: Eight subjects in each group completed 3 weeks of SIT. In both the COPD and healthy group, no significant changes found in peak stroke volume (SVpeak; $p = 0.66$ vs $p = 0.71$, respectively) and peak cardiac output (COpeak; $p = 0.68$ vs $p = 0.47$, respectively) during incremental exercise test. The results showed significant decrease in resting systolic blood pressure (SBP) in both COPD (139.1 ± 15.0 mmHg vs 130.6 ± 9.7 mmHg, $P = 0.04$) and healthy (128.6 ± 9.4 mmHg vs 122.8 ± 11.0 mmHg, $p = 0.02$) groups. The analysis showed a dramatically improvement in aerobic performance during cycle time to exhaustion (TTE) in both groups (COPD, 460.3 ± 361.5 sec vs 686.8 ± 511.3 sec, $p = 0.04$, Healthy, 489.3 ± 343.6 sec vs 831.0 ± 492.8 sec, $p = 0.009$). Peak power output (PPO) increased significantly from the second to the last SIT session in COPD and healthy groups (14.0% $p < 0.01$ vs 18.8% $P = 0.01$, respectively).

Conclusion: Short-term SIT is insufficient to improve central adaptations for SV and CO during exercise despite reduced peripheral vascular resistance at rest and improved aerobic performance during cycle to exhaustion with COPD patients and healthy elderly individuals.

Keywords: Cardiovascular function, Stroke volume, COPD, Sprint interval training

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Abbreviations

A-VO_2	Arteriovenous oxygen difference
CO	Cardiac output
COend	Cardiac output at the end of incremental exercise
COPD	Chronic obstructive pulmonary disease
COpeak	Peak cardiac output
DBP	Diastolic blood pressure
EFL	Expiratory flow limitation
HIIT	High-intensity interval training
HR	Heart rate
PR	Pulmonary rehabilitation
PPO	Peak power output
PWR	Peak work rate
SBP	Systolic blood pressure
SIT	Sprint interval training
SV	Stroke volume
SVend	Stroke volume at the end of incremental exercise
SVpeak	Peak stroke volume
TTE	Time to exhaustion
VO_2	Oxygen uptake
VO_2max	Maximal oxygen uptake
VO_2peak	Peak oxygen uptake

Introduction

Exercise training is a principal component of pulmonary rehabilitation in chronic obstructive pulmonary disease (COPD) patients because it reduces the severity of respiratory symptoms such as dyspnea (Rochester, 2003). Additionally, it improves exercise tolerance and health-related quality of life (Rochester 2003). The deterioration of lung function and mechanics in COPD is a major limitation, not only to exercise training, but also functional daily activities. There are minimal changes in lung function in response to exercise training in general and in particular endurance training. However, cardiac and skeletal muscle function can improve (Rochester 2003; Ramponi et al. 2013; Bronstad et al. 2013). Therefore, it is essential to implement exercise training in pulmonary rehabilitation to improve functional capacity without the aggravation of lung function during exercise.

According to the last statement of global initiative for obstructive lung disease (GOLD), "COPD is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases" (Global Initiative For Obstructive Lung Disease 2018). It is one of the main causes of mortality and morbidity worldwide (Rabe et al. 2007), and currently the fourth leading cause of death in the world (Rafael et al. 2012) and estimated to be the third by 2020 (Mathers and Loncar 2006). The major symptoms of COPD are chronic progressive dyspnea, cough, and sputum production, and these symptoms lead to airflow limitation. COPD is classified into four stages depending on the degree of airway obstruction represented from mild to very severe (Rabe et al. 2007).

Expiratory flow limitation (EFL) and lung hyperinflation are common pathophysiological signs of COPD as a result of marked airway obstruction (O'Donnell and Laveneziana 2006). In healthy subjects, there is an increase in demand for blood flow and oxygen uptake in respiratory and locomotor muscles during intense exercise. This demand is met by increasing the amount of oxygen uptake in the lungs mediated through an increase in cardiac output (CO, amount of blood pumped by the heart every minute) and arterio-venous oxygen difference (A-VO_2) i.e., skeletal muscle oxygen extraction from the blood (Hickam and Cargill 1948). Collectively, the Fick equation can summarize the limitation of oxygen uptake through oxygen delivery and extraction during maximal exercise; $VO_2max = CO \cdot$ arterio-venous oxygen difference (A-VO_2).

In COPD, airway obstruction and EFL cause an increase in the oxygen cost of breathing at rest and exercise, i.e. increased breathing effort and pattern (Aliverti and Macklem 2001). COPD is a systemic and heterogenic disease where respiratory symptoms, in terms of dyspnea and dynamic hyperinflation aggravated with effort, and can be associated with cardiovascular disorders (Tzani et al. 2011). Thereby, introducing exercise training with COPD patients need to address new modalities to improve exercise tolerance and reduce cardiovascular risks without the aggravation of respiratory symptoms.

Cardiovascular changes in COPD

In addition to lung disease, several patients with COPD have cardiovascular disturbances. Cardiovascular risk is a leading cause of mortality in patients with COPD. COPD can be a major risk factor of ischemic heart disease. The mechanism of cardiovascular disease with COPD is poorly understood. However, systemic inflammation associated with COPD might be a potential mechanism for the development of cardiovascular risk, which found to be associated with increased systemic oxidative stress, endothelial dysfunction, and atherosclerosis (Macnee et al. 2008). The primary hemodynamic abnormality in COPD is pulmonary hypertension mediated through alveolar hypoxemia and increased pulmonary vascular resistance, which in turn lead to increased right ventricular afterload (Aliverti and Macklem 2001; Sietsema 2001; Rogers and Howard 1992). Thereby, pulmonary hypertension can lead to right ventricular dysfunction in the absence of coronary artery disease (Morrison 1987).

Exercise limitation in COPD

Exercise intolerance is a common symptom of COPD, which potentially leads to physical inactivity and poor health status (O'Donnell and Webb 2008). The complex interaction between central factors such as ventilation, dynamic hyperinflation, and dyspnea with peripheral factors like muscle atrophy, weakness, and fatigue are the main causes of exercise intolerance in COPD (Debigare and Maltais 2008). Dynamic hyperinflation is described by the accompanying increase in end-expiratory lung volume during physical effort i.e., reduced elastic recoil of the lung during exercise (Thomas et al. 2013). Dynamic hyperinflation has been associated with dyspnea in patients with moderate COPD (Sabapathy et al. 2004). It has been demonstrated that COPD patients with hyperinflation have low CO associated with low stroke volume (SV, amount of blood pumped by heart every beat) and maximal oxygen

uptake (VO_2max) during exercise which in turn reduce exercise tolerance(Stewart and Lewis 1986). VO_2max is defined by Hill et al. as the maximum amount of oxygen the body use during intense exercise, when no further increase in effort can raise it i.e., reaching a plateau with increasing workload (Hill and Lupton 1923). While peak oxygen uptake (VO_2peak) is the highest oxygen uptake attained upon maximal exercise test, designed to bring the subject to the limit of tolerance (Whipp 2010). In healthy subjects, maximal CO is a primary limitation for VO_2max during maximal exercise (Bassett and Howley 2000). Taken together, there are three major determinants of endurance performance; VO_2max, work economy and lactate threshold. Work economy is the amount of oxygen uptake during standard workload, while lactate threshold is the workload where there is excess lactate production in the blood compared to removal (Bassett and Howley 2000).

In COPD, reduced oxygen saturation and increased respiratory effort due to airway obstruction can interrupt the chain of oxygen delivery and oxygen extraction during exercise. In other words, central and peripheral factors can be worsened during submaximal and maximal exercise leading to exercise intolerance and physical inactivity. Overall, there are three major limitations that contribute to the exercise intolerance in COPD patients: (1) increase oxygen cost of breathing due to airways obstruction, (2) skeletal muscle dysfunction, (3) dynamic hyperinflation associated with reduced SV and/or CO (Aliverti and Macklem 2001; Debigare and Maltais 2008; O'Donnell and Webb 2008). Referring to COPD as a heterogenic and systemic disease, some of these limitations may dominate according to the severity of symptoms and disease stage. The detailed explanation of the primary exercise limitation among these limitations in different stages of COPD is beyond the scope of this study.

Cardiovascular limitation during exercise with COPD

In COPD, the main limitation of increased CO during exercise is (1) right heart dysfunction due to increased right ventricular afterload induced by pulmonary hypertension, (2) Exercise-induced hyperinflation (Morrison 1987; Aliverti and Macklem 2001; O'Donnell and Webb 2008). In general, CO is a strong determinant of oxygen delivery in healthy individuals and COPD patients during exercise to meet the metabolic demand of skeletal muscles. Cardiac output is the product of heart rate (HR) and SV (Vincent 2008). The effect of exercise training on CO is governed by SV with minimal change in heart rate. There are three major determinants of SV: ventricular filling (preload), myocardial contractility, systemic and

pulmonary vascular resistance (afterload) (Vincent 2008). In COPD, cardiovascular adaptation during exercise is likely limited by pulmonary hypertension and lung hyperinflation (see below for details).

It has been shown that COPD patients with dynamic hyperinflation have a poor cardiovascular function during exercise (Tzani et al. 2011). In addition, exercise-induced hyperinflation elicits increased intrathoracic pressure and, consequently, reducing venous return to the heart i.e. hypovolemia that might progressively decrease filling of the left ventricle. Therefore, reduced CO and/or SV with COPD patients might occur during exercise (Aliverti and Macklem 2001; Sietsema 2001; Rochester 2003; O'Donnell and Webb 2008; Ramponi et al. 2013). Nevertheless, there are some groups of COPD that are not characterized by dynamic hyperinflation during exercise (O'Donnell et al. 2001; Aliverti et al. 2005). In the latter group, pulmonary hypertension is likely the main limitation to increased cardiac output during exercise because of increased right ventricle afterload. Moreover, increased SV in response to exercise training is possibly related to improvement in ventilation during exercise with COPD patients (Ramponi et al. 2013). It has been reported that poor oxygen transport to skeletal muscles due to low SV is likely the main limitation of aerobic capacity in COPD patients (Minh et al. 1979). Consistent with this, Inoue et al. reported a strong association between decreased left ventricular SV and reduced exercise tolerance in stable COPD patients (Inoue et al. 2017). In addition, the severity of COPD is possibly responsible for reduced cardiac function (Bogaard et al. 1998). Thus, the heart-lung interaction and impaired cardio-circulatory function is likely a sub-clinical exercise limitation associated with dynamic hyperinflation in COPD patients. Thereby, this interaction needs to be addressed further during pulmonary rehabilitation of COPD.

Exercise training in Pulmonary rehabilitation

Exercise training is a cornerstone of pulmonary rehabilitation to improve physical function with COPD patients. Pulmonary rehabilitation (PR) is multiple intervention programs that include, but are not limited to, exercise training, education, and behavior change, and designed to improve the physical and psychological status of patients with chronic respiratory disease (Spruit et al. 2013). Exercise training with COPD patients mainly includes endurance and strength training and is found to improve exercise tolerance, health-related quality of life, and exercise capacity (Coppoolse et al. 1999; Vogiatzis et al. 2002; Bjorgen et al. 2009;

Rochester 2003). The incorporation of strength and endurance training to PR a program increases muscle strength and muscle mass (Ries et al. 2007).

Aerobic endurance training is defined as dynamic exercise training involving major muscle groups for several minutes such as running, bicycling, and swimming where the aerobic system covers the main part of energy expenditure (Clausen 1977). The primary aim of endurance training with COPD patients is to improve aerobic capacity as aerobic activities are part of their daily life activities (Gloeckl et al. 2013). Pulmonary rehabilitation recommendations of endurance training; progressed as tolerated to reach 30-40 min at intensity 60-70% of peak work rate (PWR), for 3-4 days per week (Gloeckl et al. 2013)

In COPD, moderate aerobic training (75% PWR and 80% HRpeak) with cycle ergometer has shown improvement in submaximal exercise endurance performance with minimal despite no changes in VO_2peak reported (Pitta et al. 2004; Porszasz et al. 2005).

Cardiovascular adaptations to exercise training in COPD

In healthy subjects, exercise training improves central adaptations through the oxygen transport capacity of the circulatory system and peripheral adaptations through the oxidative capacity of the skeletal muscles. Consequently, these changes enhance the organism's VO_2max (Clausen 1977). Cardiac output and A-VO_2 are the main factors that determine VO_2max. The increase in cardiac output is reflected by changes in stroke volume and/or heart rate (Daussin et al. 2007). Increase in heart contractility and ventricular filling are major determinants of stroke volume in humans during exercise (Higginbotham et al. 1986). Cardiac bradycardia during rest and submaximal training are signs of a cardiovascular training effect (Blomqvist and Saltin 1983). The reduction in CO in response to exercise training reflects an increase in oxygen extraction by skeletal muscle during submaximal exercise (McArdle et al. 2010). Exercise training increases maximal CO through enhanced myocardial contractility and improves blood flow to trained skeletal muscles associated with reduced peripheral vascular resistance (Clausen 1977).

In COPD patients, exercise training is found to enhance cardiovascular function associated with an improvement in ventilatory function and reduction of dynamic hyperinflation (Ramponi et al. 2013; Nasis et al. 2015). Moreover, pulmonary rehabilitation including strength and endurance training may reduce cardiovascular risks in COPD patients by reducing arterial stiffness and blood pressure, i.e. markers of cardiovascular risk (Vivodtzev et al. 2010; Gale et al. 2011). Additionally, continuous endurance training reduced arterial stiffness and blood pressure associated with an improvement in exercise performance during

6-minute walk distance, despite no changes in VO_2peak in COPD patients (Vivodtzev et al. 2010). Conversely, pulmonary rehabilitation with upper and lower body cycling performed with COPD patients improved VO_2peak and blood pressure without changes in endothelial function and arterial stiffness (Gelinas et al. 2017). These different findings may be attributed to the heterogeneity of the disease itself. Where, the systemic inflammation of COPD may aggravate cardiovascular risks. In addition, these previous findings have not assessed SV and CO changes in response to endurance training. Also, different training interventions may contribute to these controversial findings in response to endurance training in COPD patients. Further research is needed to investigate the central haemodynamics adaptations to endurance training in all stages of COPD.

High-intensity training

The responses to any exercise training program are mainly guided by the following four major parameters: training intensity; training frequency; training duration and initial fitness level (McArdle et al. 2010). Exercise intensity is an essential factor for improving VO_2max secondary to SV in young trained men (Helgerud et al. 2007). Moderate continuous training is prolonged aerobic training at submaximal intensity (~ 60-80% VO_2max) (McArdle et al. 2010). Interval training can be classified into high-intensity interval training (HIIT) and sprint interval training (see pages 12-13 for sprint interval training). High-intensity interval training is a method of training that elicits ≥ 80% of maximal heart rate throughout alternating periods of high and low-intensity exercise, which might be an alternative training method to sustain high-intensity training (Rochester 2003; MacInnis and Gibala 2017). It has been shown that HIIT is superior to moderate intensity continuous training for improving VO_2max and cardiac function in healthy individuals (Helgerud et al. 2007) and heart failure patients (Wisloff et al. 2007; Haykowsky et al. 2013). However, in COPD patients, improvements in VO_2peak and cardiac function were similar after HIIT (four 4-minute bouts at 90-95% of maximal heart rate) compared with moderate intensity training (60-70% of maximal HR). These changes were expressed in increased SV and improvement of left ventricular systolic function (Bronstad et al. 2013). High-intensity and moderate-intensity training are likely to have equal effects with improving VO_2peak and heart function in COPD patients (Beauchamp et al. 2010; Bronstad et al. 2013). The lack of superiority of HIIT vs. moderate continuous training in improving VO_2max in COPD may be because of the lung functions are the limiting factor in COPD patients. Indeed, some COPD patients can get dyspnea and lung hyperinflation

shortly after starting a high-intensity exercise. This can limit their performance with less adaptation to the intensity of the training. A repeated very short (≤ 60 secs) maximal or supramaximal intensity bouts may induce optimal cardiovascular adaptations before dyspnea and hyperinflation worsen during exercise. There are few controlled studies in the literature investigating the effect of interval training on cardiovascular function in COPD patients. Further studies need to investigate the effect of interval training on cardiovascular changes in COPD during rest, submaximal, and maximal exercise to have a full figure of cardiac adaptations after high-intensity training.

Short interval training with COPD

Based on the nature of COPD as heterogenic and systemic diseases, it can be challenging to implement high-intensity training during pulmonary rehabilitation. The practical recommendation of short interval training in PR is < 60-sec exercise at 80% of PWR interspersed with 20-30 sec rest, progressed as tolerated to reach 80-150% of PWR, 3-4 days per week (Kortianou et al. 2010). Indeed, short interval training with COPD patients has shown improvement in exercise tolerance and health-related quality of life (Vogiatzis et al. 2002; Puhan et al. 2006). Moreover, in patients with very severe COPD, short interval training (< 60 sec at 80-100% of peak workload) found associations with fewer symptoms of dyspnea and less peripheral muscle discomfort during exercise and rest compared to continuous training at constant load (Vogiatzis et al. 2002; Puhan et al. 2006). On another note, these previous studies did not assess aerobic capacity or metabolic adaptations after the recommended short interval training. However, Nasis et al. reported improved VO_2peak along with peak CO after short interval training (30 sec work / 30 sec rest) at 100% of PWR. This was associated with mitigation of dynamic hyperinflation during constant-load (75% PWR) exercise (Nasis et al. 2015). In the abovementioned study by Nasis et al., short interval training was incorporated in a PR program including breathing exercises and supplemental oxygen breathing during training. Further studies are needed to investigate physiological adaptations of isolated short interval training in COPD patients alongside exercise capacity and quality of life.

Sprint interval training

Sprint is maximal exercise bouts less than 1-minute duration, where the main energy expenditure is covered by the anaerobic energy system (Clausen 1977). Sprint interval training (SIT) is a modality of interval training. The origin of SIT started from repeated Wingate test that consists of 30 seconds ‘all-out' efforts cycling against the resistance of 7.5% of body weight (MacInnis and Gibala 2017). The Wingate anaerobic test is the most extensively used test for assessing human muscle capacity to generate power from anaerobic energy systems (Vandewalle et al. 1987). SIT has been modified to involve bouts of 10-30 seconds supramaximal effort against resistance of 5.0% of body weight at intensities greater than VO_2max by all-out or supramaximal efforts (Hazell et al. 2010; Gillen et al. 2016).

There is a growing body of evidence that SIT can improve both aerobic and anaerobic capacity including VO_2max, time trial performance, peak power output and mitochondrial enzymes in healthy sedentary and active population (MacDougall et al. 1998; Hazell et al. 2010; Sloth et al. 2013; Gillen et al. 2014; Matsuo et al. 2014). However, the mechanism behind the improvement of VO_2max with SIT is yet uncertain and needs further investigations (Sloth et al. 2013). SIT has shown significant improvement to the oxidative capacity of skeletal muscles alongside with mitochondrial and enzymatic function associated with marked improvement in exercise capacity (Sloth et al. 2013). Few studies measured skeletal muscle capacity combined with cardiovascular changes in response to SIT and the results are controversial (Macpherson et al. 2011; Trilk et al. 2011). Some studies reported improvement in stroke volume during rest and submaximal exercise after SIT (Trilk et al. 2011; Matsuo et al. 2014; Zhang et al. 2019). Sprint interval training may elicit acute physiological adaptations through the strain placed on the cardiovascular and metabolic system by inducing near maximal cardiovascular response during and immediately after training (Freese et al. 2013). Nevertheless, it has been suggested that the very short sprint bouts (20-30 secs) during SIT are insufficient to improve cardiovascular function in healthy subjects (Macpherson et al. 2011). Moreover, it has been reported that the training dose of SIT i.e., sprint duration and training frequency, has incidence for response in VO_2peak following SIT in young adults (Gurd et al. 2016).

Recently SIT has been introduced to some patient populations such as non-alcoholic fatty liver disease and Type II diabetes. These studies reported some physiological adaptations through the increase in VO_2peak and insulin sensitivity (Heiskanen et al. 2017; Sargeant et al. 2018). In addition, there is a considerable body of evidence that SIT can enhance peripheral

vascular resistance mediated through reduced systolic and diastolic blood pressure with sedentary and old subjects (Heiskanen et al. 2017; Holloway et al. 2018; Adamson et al. 2018; Whyte et al. 2010). Moreover, SIT has been shown to improve arterial distensibility and endothelial function in young healthy individuals (Rakobowchuk et al. 2008). Taken together, SIT may improve cardiovascular function and aerobic capacity in a sedentary and clinical population. Further studies needed to investigate the optimal dose of SIT required for different population.

SIT with COPD

To the best of the author's knowledge, no single study has been carried out SIT on COPD patients. Overall, some patients with severe COPD are not able to sustain high-intensity exercise due to exercises limiting symptoms, such as dyspnea and leg pain (Maltais et al. 1997). Accordingly, they may not gain the physiological adaptation of the high-intensity training because of ventilatory limitation, i.e., increased their ventilator demand during exercise, which in turn reduce the heart contractility because of pulmonary hypertension and increased ventricular afterload. There is a considerable body of evidence that the recommended short interval training is feasible and an effective mode of endurance training with COPD patients in order to sustain high-intensity training, especially in patients with severe COPD (Puhan et al. 2006; Kortianou et al. 2010; Gloeckl et al. 2013). The nature of SIT with short bouts (20-30 secs) is similar to the recommended short interval training with COPD, however, it differs by the supramaximal intensity and long active recovery (3-5 minutes). The major rationale for using SIT in COPD is that the patients can achieve supramaximal intensity before stopping exercise due to dyspnea and/or fatigue with a potential improvement in cardiorespiratory function induced by all-out efforts.

Aim and hypothesis

The primary aim of the current study is to investigate the effect of SIT on aerobic performance during cycle TTE, and on VO_2peak. And whether the mechanism behind this effect is attributed to central adaptations in terms of SV and CO in COPD patients and elderly healthy individuals during rest and exercise. A secondary aim is to examine whether SIT could reduce resting blood pressure in both groups. There is a promising improvement in the aerobic capacity associated with an increase in SV during exercise in sedentary and healthy

individuals in response to SIT and short interval training (Trilk et al. 2011; Esfandiari et al. 2014). In line with this, COPD patients have a very low exercise tolerance and aerobic capacity compared to the latter populations. Therefore, we tested the hypothesis that short-term SIT in COPD patients would improve aerobic performance during cycle TTE accompanied by an increase in SV and CO during maximal exercise with no changes during rest.

Methods

Subjects

Ten patients with a stable stage of COPD according to GOLD guidelines (Global Initiative For Obstructive Lung Disease 2018) were recruited from the outpatient ward of the lung department at St Olav university hospital. Inclusion criteria included, no resting hypoxemia, age > 50 years and post bronchodilator FEV_1< 60%. Patients with known heart disease or any other medical condition limiting exercise training were excluded. EEG was recorded at baseline to exclude signs of ischemic heart disease, arrhythmias, and conduction disorders and thereby ensure safe training for the patients. Patients having participated in a pulmonary rehabilitation program during the last 3 months were excluded. Nine age-matched healthy subjects were recruited to the study for participating in SIT program and serving as a control group. The study was approved by the regional committee for research ethics (2018/723/REK nord) and is registered in the clinical trials database (NCT03735615). All participants provided written, informed consent.

Experimental design

Three testing days were performed before and after a three-week training program. The first visit was for familiarization of the subjects to the exercise test and to find an optimal standard workload, 12-13 on the Borg 6-20 scale (Borg 1982). In the second day, the aerobic capacity and cardiovascular function were assessed by performing an incremental exercise test on a cycle ergometer. The last testing day assessed aerobic performance by performing cycle time to exhaustion test (TTE). At least 48 hours separated between TTE and the first training session. Vigorous activity was discouraged 24 hours before the exercise test and training. The post intervention measurements were conducted no earlier than 48 hours and no later than 96 hours after the last training session.

Day 1

The first visit to the laboratory involved familiarization with the exercise test, the laboratory and determination of work economy (standard workload) on a bike from ratings of perceived exertion (RPE; Borg 12-13 scale).

Day 2

The testing day initially started with measuring blood pressure then central hemodynamics by impedance cardiograph during rest. Afterward, the aerobic capacity combined with central hemodynamics were assessed during work economy and incremental exercise test.

Day 3

Cycle TTE was performed to the limit of tolerance at 80% of the previously determined peak power at the end of the incremental exercise test. Subjects started with 5 minutes warm up then they were motivated to cycle until exhaustion. The test was terminated when the number of revolutions per minute (RPM) dropped below 40 and the endurance time was measured. Heart rate was recorded by a heart rate monitor (Polar Electro, Kempele, Finland).

Cardiopulmonary exercise tests

All the exercise tests and training were performed on an electromagnetically braked cycle ergometer (Corival, Lode B.V., Groningen, the Netherlands) using a computer-based breath-by-breath cardiopulmonary exercise testing system (MetaMax II Leipzig, Germany). Volume and gas analyzers were calibrated before testing. Work economy was defined as oxygen uptake at a submaximal workload (RPE; Borg 12-13 scale) determined during the first familiarization visit. Patients and healthy subjects performed the previously determined work economy for 5 minutes then progressed to incremental exercise test, (5-10 W/min in patients and 15-20W/min with healthy individuals to limit of tolerance). Oxygen uptake and minute ventilation were recorded as the average of 10 seconds of data. Arterial oxygen saturation was monitored continuously for the COPD group. Peak work rate (PWR) is defined as the maximum load which subjects maintained cycling for complete 30 seconds. VO2peak values for incremental cycling were identified as the average of the three highest consecutive 10-seconds values obtained at the last stage of incremental exercise.

Central haemodynamics

Heart rate (HR), stroke volume (SV), and cardiac output (CO) measured by signal morphology impedance cardiograph (SM-ICG) device (PhysioFlow®, PF-05 Lab1, Manatec Biomedical, France) during rest and exercise. The PhysioFlow device and its methodology have been described earlier (Charloux et al. 2000; Richard et al. 2001). Briefly, the system emits a high-frequency (75 kHz) and low-intensity (3.8 mA) current via chest surface electrodes (Ambu® BlueSensor R, Denmark). This system uses changes in transthoracic impedance in response to an administered electrical current during cardiac ejection to calculate stroke volume. To the difference of conventional ICG systems, SM-ICG does not require the assessment of the potentially unreliable chest impedance baseline (Z0) to measure SV. Moreover, it features a high-performance signal stabilization filter (HD-Z^{TM}) that cleans waveforms from noise during exercise. Two sets of electrodes, each set consist of one "transmitting" electrode, one "sensing" electrode, one set applied above the supraclavicular fossae lateral to the left base of the neck (Z1 & Z2) and the other set applied at the same level of the xiphoid bone during rest (Figure 1), and dorsally along the spine (Z3 & Z4) during exercise (Figure 2). In addition, two electrodes were used to measure a single ECG signal placed on the breast area (EKG1 & EKG2). Initially, an alcohol swab was used to clean the neck, right chest, trunk at V6, and spine, and then a skin preparation abrasive gel (NuPrep, Weaver and Company, Aurora, CO, USA) was rubbed into these areas and the skin was further cleaned with a paper towel. The leads were taped to the skin and subjects were asked to wear a net vest (Surgifix®, Italy) during the exercise test to reduce movement of the leads. Before each recording, the system was auto-calibrated following a 30-beat procedure with consideration of height, body weight, and blood pressure values. This method showed validity against the Fick method during rest and exercise in healthy subjects (Richard et al. 2001) and COPD patients (Charloux et al. 2000)

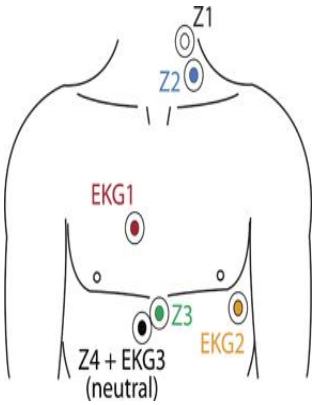

Figure 1 *Placement of electrodes during rest (Physioflow User Manual 2016)*

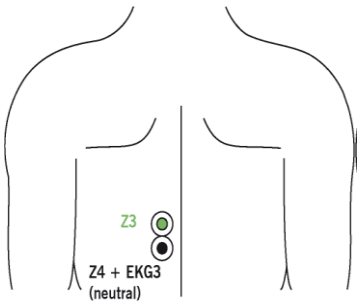

Figure 2 *Placement of electrodes during exercise (Physioflow User Manual 2016)*

Cardiac output is based upon the following formula: CO (l/min) = HR (beats/min) × SVi (ml/m^2) × BSA (m^2). where, HR is heart rate based on R–R interval measurement determined from the ECG first derivative dECG/dt, which provides a more stable signal than the ECG signal itself BSA is body surface area calculated from the Haycock formula

(BSA= 0.024265 × body mass$^{0.5378}$ × height$^{0.3964}$) and SVi is the stroke volume index (SV/BSA) described the ability of the heart to eject flow regardless of body size.

Rest

Subjects were asked to rest in a sitting position for five minutes before measuring blood pressure. Blood pressure measurement was performed using automated sphygmomanometer (Casmed™ 740, USA) before calibration of the physioflow at rest and exercise. Blood pressure was measured twice at least. One measurement was taken for blood pressure from each arm in a sitting-supported position, and the highest recording of the two nearest values (≤ 5 mmHg) between the two arms was selected for analysis as recommended for initial examination (Pickering et al. 2005). Resting hemodynamics were recorded while the subjects were lying supine on a bench resting for 10 minutes in a quiet room with low light. Resting variables were identified as the average of any 2 minutes in a steady state as previously reported (Hargens et al. 2015)

Exercise

Central haemodynamics measurements during maximal exercises test were synchronized to start with MetaMax analyzer to start recording at the same time. Submaximal SV and CO were identified as the highest average of any consecutive 30 seconds period by the last minute of the work economy (12-13 Borg scale). Submaximal and peak HR were the highest average of over 10 seconds heart rate attained at work economy and at the end of incremental exercise test respectively. Peak SV can be attained at submaximal workload in healthy individuals and COPD patients (Vella and Robergs 2005; Louvaris et al. 2019). Accordingly, peak values for SV and CO were identified (SVpeak, COpeak respectively) as the highest average of any consecutive 30 sec period with stable and strong signal quality during the incremental exercise. In addition, values of SV and CO at VO_2peak were identified as SVend and COend respectively. A-VO_2 was estimated at the end of work economy and at VO_2peak from Fick equation by using the following formula, A-VO_2 = VO_2/CO and expressed in ml O_2/dl blood. Heart rate recovery (HRR) was recorded as the difference between HR at peak effort minus heart rate after 1 minute of recovery.

Training program

COPD patients and age-matched control subjects were recruited for 3 weeks of SIT training. SIT (3 sessions/week), consisted of 4 sprints of 20 seconds duration and 3-5 minutes active recovery between the sprints. The aim of the first training session was to familiarize the subjects with SIT and determine optimal resistance and recovery time. Subjects started warm-up by cycling 5 minutes at the previously determined workload (12-13) on a Borg scale. Then they repeated 4 sprints bouts with "all out" efforts at a resistance of 4-6% of body weight interspersed with 3-6 minutes recovery at low intensity (20-40 watt) in patients and (60-80 watt) in healthy subjects depends on the severity of the symptoms in patients and the fitness level of the healthy subjects. Rest (1-2 min) was allowed for some participants who cannot sustain cycling immediately after sprints then active recovery encouraged. The highest peak power output (PPO) was selected over the 4 sprints in the second and ninth session for analysis. The recovery time between intervals was gradually reduced in the COPD group as the training progressed and kept constant at 3 minutes in the healthy subjects. All participants were encouraged to cycle at 70 RPM before (~30 sec) sprints then encouraged with maximal speed and power during the sprint. In the COPD group, two subjects didn't tolerate the reduction of recovery in the last week of training. Accordingly, the recovery time was kept the same from the first training session with these subjects. There was no cooldown performed after the training session. The total training duration including warm-up was 16-18 minutes with healthy subjects and 18-20 minutes with COPD patients.

Statistical analysis

Data are represented as mean ± standard deviation (SD) and were analyzed using SPSS Version 25 (Chicago, IL, USA). Normality of the data was assessed using Shapiro-Wilk test. Paired t-test was performed to assess the difference in both groups before and after training. Pearson correlation performed between ΔTTE and ΔPPO. Statistical significance was established at ($P < 0.05$).

Results

Participant characteristics

Baseline parameters and anthropometric measurements are presented in Table 1. There was no significant difference in weight, BMI, and age post training within groups. No adverse cardiovascular events were reported by any participants during and after SIT. Three subjects were excluded from post analysis; two from the COPD group due to non-adherence and sickness not related to the training program and one from the healthy group due to non-adherence to the training intervention.

Table 1 *Baseline physical characteristics of COPD and healthy participants (mean ± SD)*

Parameter	COPD	Control
Age (years)	70.7 ± 7.7	65.4 ± 3.6
Gender (M/F)	3/7	3/6
Weight (kg)	68.3 ± 19	80.6 ± 14.2
Height (cm)	172.0 ± 10.7	172.3 ± 8.9
BMI (kg/m^2)	22.7 ± 4.3	27.1 ± 4.5

M: male; F: female; BMI: body mass index

Cardiovascular function during Rest

There was no significant difference ($P > 0.05$) in HR, SV, and CO during rest in both groups (Table 2). A significant reduction of SBP in both the COPD (-6.1%, $p = 0.04$) and healthy group (4.8%, $p = 0.02$). No significant change of DBP was observed in any group, but it tended to decrease ($p = 0.09$) in the healthy group (Figure 3).

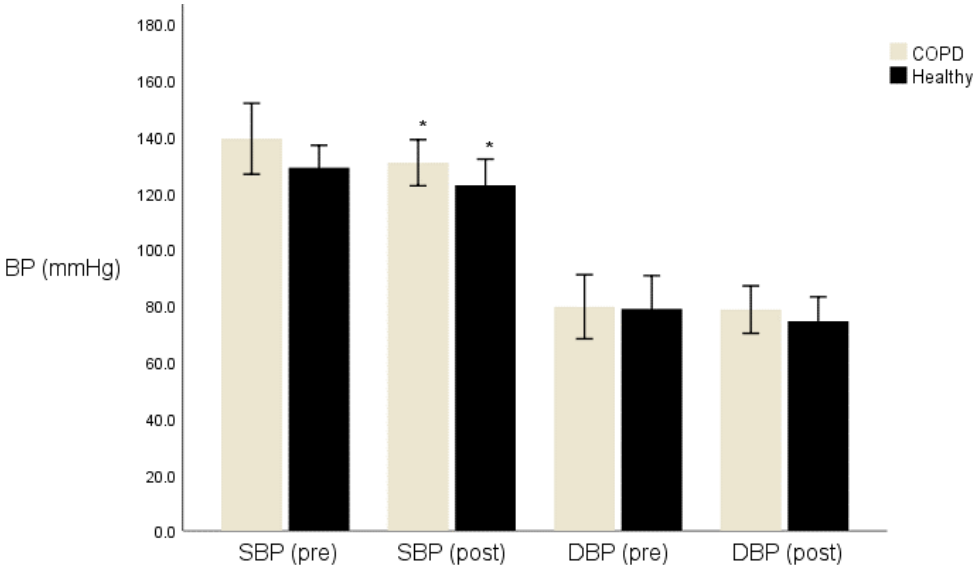

Figure 2 *Systolic blood pressure, DBP = Diastolic blood pressure. The bar graph represents the change of SBP and DBP during rest before and after SIT, * = P < 0.05.*

Cardiorespiratory function at submaximal and maximal exercise

No significant changes ($p > 0.05$) found in all cardiorespiratory variables during work economy (Table 2). Heart rate during work economy was reduced in both COPD and healthy group (-4.0% vs -4.1%, respectively) with no statistical significance ($p > 0.05$). The data at submaximal work rate for one subject were excluded in the COPD group because of panic with wearing the mask which most likely overestimated HR, accordingly CO and VO_2. Where the maximal exercise test for this subject was done on a different day with mouthpiece instead. There was a tendency ($p = 0.09$) of increased VO_2peak in the healthy group with no significant changes in the COPD group ($p = 0.26$). The A-VO_2peak did not change significantly in COPD and increased (11%) in the healthy group with no statistical difference ($p > 0.05$).

During incremental exercise test, no significant change ($p > 0.05$) was found in SVpeak and COpeak with the COPD or healthy group (Table 3). In the end of incremental exercise at VO_2peak, SVend and COend did not change significantly ($p > 0.05$) in both groups (Table 3). The data of SVend and COend were excluded from two subjects in the healthy group because of weak signal quality. PWR increased significantly (199.3 ± 62.1 W vs 212.5 ± 62.1 W, $p = 0.004$,) in the healthy group, whereas there was a tendency of significant increase in COPD group (75.0 ± 29.6 W vs 84.3 ± 39.0 W, $p = 0.06$). HRR did not change in COPD group (11.6 ± 7.3 beat/min vs 11.2 ± 9.7 beat/min, $p = 0.80$) and in healthy group (28.3 ± 5.5 beat/min vs 29.7 ± 4.5 beat/min, $p = 0.22$) with no statistical difference**.**

Table 2 *Cardiorespiratory changes in both healthy and COPD groups before and after SIT; during rest, submaximal, and peak exercise.*

	COPD			***Healthy***		
Parameter	***Pre***	***Post***	***P-Value***	***Pre***	***Post***	***P-Value***
Rest						
HR (beat/min)	*72.2 ± 12.1*	*73.6 ± 16.2*	*0.60*	*57.7 ± 6.1*	*60.0 ± 6.7*	*0.28*
SV (ml/beat)	*83.3 ± 28.3*	*84.0 ± 29.3*	*0.78*	*107.7 ± 18.3*	*105.6 ± 21.7*	*0.53*
CO (l/min)	*5.8 ± 1.4*	*5.8 ± 1.1*	*0.95*	*6.1 ± 0.8*	*6.2 ± 0.7*	*0.70*
Submaximal						
HR (l/min)	*107.5 ± 17.0*	*103.1 ± 18.2*	*0.37*	*121.1 ± 21*	*116.1 ± 15.4*	*0.26*
SV (ml/beat)	*92.3 ± 20.9*	*94.1 ± 18.7*	*0.75*	*130.0 ± 25.6*	*128.5 ± 32.9*	*0.88*
CO (l/min)	*9.8 ± 2.7*	*9.3 ± 1.4*	*0.55*	*15.3 ± 1.7*	*14.6 ± 3.4*	*0.35*
VO_2 (l/min)	*0.7 ± 0.3*	*0.8 ± 0.2*	*0.26*	*1.5 ± 0.4*	*1.5 ± 0.3*	*0.75*
VO_2 (ml/kg/min)	*11.4 ± 3.8*	*12.0 ± 3.5*	*0.22*	*19.1 ± 4.6*	*19.5 ± 4.3*	*0.57*
A-VO_2 (ml/dl)	*7.9 ± 2.3*	*8.7 ± 1.9*	*0.26*	*10.0 ± 2.4*	*11.0 ± 2.7*	*0.29*
VE (l/min)	*31.8 ± 10.4*	*32.3 ± 9.9*	*0.62*	*45.0 ± 12.8*	*44.8 ± 13.2*	*0.88*
Peak						
HR (beat/min)	*138.8 ± 22.8*	*138.6 ± 21.0*	*0.93*	*162.5 ± 11.5*	*164.6 ± 10.3*	*0.31*
A-VO_2 (ml/dl)	*8.5 ± 1.5*	*8.3 ± 2.5*	*0.80*	*10.8 ± 0.7*	*12.0 ± 2.1*	*0.14*
VO_2 (l/min)	*1.2 ± 0.4*	*1.2 ± 0.5*	*0.31*	*2.5 ± 0.9*	*2.6 ± 0.8*	*0.09*
VO_2 (ml/kg/min)	*17.3 ± 4.5*	*18.4 ± 5.5*	*0.26*	*30.7 ± 7.7*	*32.5 ± 7.0*	*0.09*
RER	*0.95 ± 0.06*	*0.96 ± 0.06*	*0.41*	*1.08 ± 0.02*	*1.09 ± 0.05*	*0.69*
SPO_2 (%)	*88.7 ± 3.7*	*89.6 ± 4.1*	*0.58*	*ND*	*ND*	*ND*
VE (l/min)	*47.6 ± 21.7*	*49.5 ± 26.0*	*0.35*	*93.1 ± 33.8*	*97.3 ± 34.3*	*0.11*

Data are mean ± SD, HR = heart rate, SV = stroke volume, CO = cardiac output, VE = Ventilation minute, HR= Heart rate, VO_2 = oxygen uptake, A-VO_2 = peak arterio-venous oxygen difference, SPO_2 = oxygen saturation, RER = respiratory exchange ratio, ND = no data, significance value = P < 0.05

Table 3 *Peak and end values of SV and CO in Healthy and COPD groups before and after SIT during incremental exercise.*

	COPD			**Healthy**		
Parameter	**Pre**	**Post**	**P-Value**	**Pre**	**Post**	**P-value**
SVpeak	105.8 ± 20.9	109.2 ± 22.6	0.66	140.4 ± 32.9	144.4 ± 31.9	0.71
SVend	101.0 ± 18.5	112.2 ± 26.1	0.23	138.5 ± 38	132.3 ± 30	0.56
COpeak	14.2 ± 3.9	13.6 ± 2.7	0.68	20.8 ± 5.9	22.0 ± 5.1	0.47
COend	13.8 ± 3.8	15.0 ± 3.6	0.30	21.6 ± 6.5	20.8 ± 5.7	0.54

SVpeak = peak stroke volume, SVend = stroke volume at the end of the incremental exercise, COpeak = peak cardiac output, COend = cardiac output at the end of incremental exercise

Time to exhaustion and Muscle force during SIT

The cycle TTE was increased significantly in both the COPD (49.2%, p = 0.04) and healthy group (69.8%, p = 0.009) (figure 4). The data for one subject in the COPD group were excluded from analysis because of incomparable workload during warm up before and after SIT. Anaerobic power represented by peak power output (PPO) increased significantly in both groups from the second to the last training session of SIT (COPD, 358.0 ± 137.0 W vs 408.2 ± 165.2 W, p = 0.007) (Healthy, 567.7 ± 205.5 W vs 674.5 ± 241.7 W, p = 0.01).

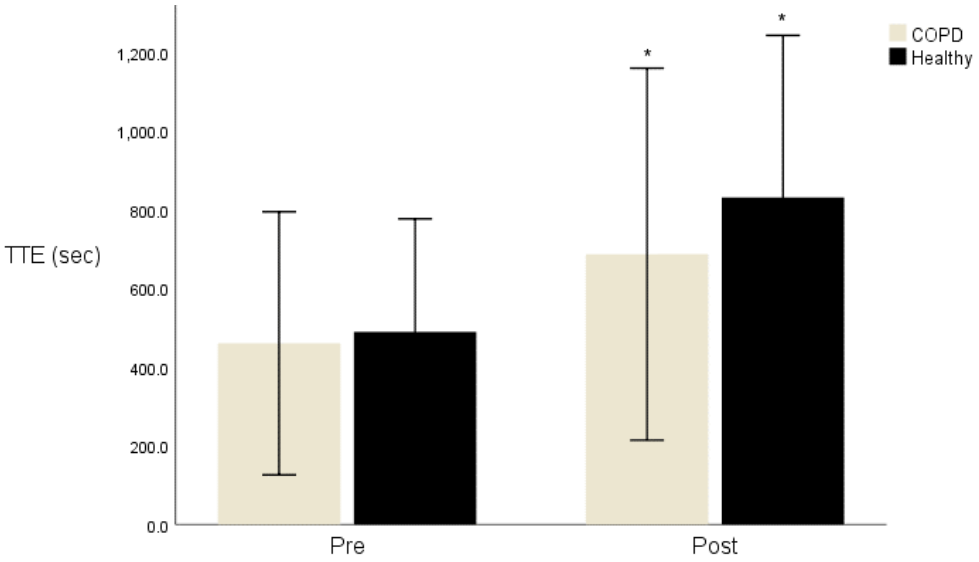

Figure 3 *TTE = cycle time to exhaustion. The bar graph represents the changes in performance during TTE before and after SIT, * = P < 0.05.*

Correlations

To examine the training effect on aerobic performance during TTE, potential mechanisms behind the improved TTE, correlation analyses were performed between the change in TTE and changes in physiological variables. There is a tendency of significant correlation between ΔTTE and ΔPPO (r = 0.72, p = 0.064) in COPD with no significant correlation in the healthy group (r = -0.40, p = 0.31).

Discussion

The major finding in the current study is the dramatic increase in aerobic performance during cycle TTE groups without changes in VO_2peak and central haemodynamics (SV and CO) during exercise in both COPD and healthy group. Interestingly, a marked reduction in resting SBP found in both groups which needs further investigation to assess the effect of SIT on peripheral vascular resistance in COPD patients and elderly individuals. Although there was a marked improvement in aerobic performance during TTE in both groups, the physiological mechanism behind this improvement is poorly understood. It can be favored to increase in anaerobic power through changes of peak power during SIT in both COPD and healthy group.

Cardiorespiratory function

There were no changes in SV and CO during rest and exercise coupled with no changes in VO_2 at work economy and maximal exercise in the current study. These results are consistent with previous findings in active healthy adults that showed improvement in aerobic performance without changes in VO_2peak (Burgomaster et al. 2005; Kavaliauskas et al. 2018). Opposed to our findings, SIT showed improvement in resting SV associated with increased VO_2peak in healthy individuals and sedentary women (Matsuo et al. 2014; Zhang et al. 2019). The disagreement between our finding and these previous findings can be mainly attributed to longer training periods (8 weeks). However, short term SIT (4 weeks) with sedentary women reported increase submaximal SV and VO_2 where the training load was progressed with an additional sprint every week (Trilk et al. 2011). Another possible discrepancy between our study and the latter finding beside the training dose that SV was estimated by using CO_2-rebreathing method during submaximal workload (50% VO_2max) for 20 minutes. It can be recommended with SIT to increase the number of bouts by one bout every two sessions as previously reported with the healthy and sedentary population (Whyte et al. 2010; Astorino et al. 2012).

In line with our findings, Macpherson et al. reported no changes in SV and CO in response to SIT with young healthy subjects (Macpherson et al. 2011). These previous reports investigated the mechanism behind improving VO_2peak whether through CO or A-VO_2. Conversely, in the present study, there were no significant changes in VO_2peak associated with no changes in CO and A-VO_2. A possible explanation for non-responding in our study can be the insufficient training dose and/or period to induce significant cardiorespiratory

adaptations. Moreover, the progression of SIT (number of bouts and recovery time) in the current study was nearly the same through 3 weeks of training without substantial progression in training load. In agreement with this, the incidence of nonresponse to SIT in VO_2peak found related to SIT dose i.e. sprint duration and training frequency (Gurd et al. 2016). It has been demonstrated that a single session of SIT can elicit submaximal VO_2 and HR (> 80% of predicted maximal values) in young healthy individuals (Freese et al. 2013). In the present study, the very short sprint (20 sec) and training period (3 weeks) do not stress the cardiorespiratory system sufficiently to induce significant central adaptation. Therefore, Further studies are required to assess the effects of various training parameters and their interaction on the training-induced physiological adaptations following SIT.

In COPD, long term exercise training (9-10 weeks) including long interval training (four 4-minute bouts at 90-95% of maximal heart rate) and short intervals at 100% PWR (30 sec work / 30 sec rest) showed improvement in resting cardiovascular function and VO_2peak associated with increase in COpeak secondary to increase in SV (Bronstad et al. 2013; Nasis et al. 2015). In COPD, limitation of increased SV and CO during exercise can be improved through increased ventricular preload and/or decreased afterload (see p.7-8 for details). The effect of SIT on this physiological chain in the current study is likely insufficient to induce central adaptation in 3 weeks. As COPD is a chronic systemic disease which may take several years to progress, it may need a longer training period and dose for inducing improvement in cardiovascular function during exercise. Interestingly, it has been shown that acute adaptation of short-term training is an increase in blood volume through plasma volume expansion after cycle interval training (eight 4-min bouts at 85% VO_2max) in young healthy subjects (Gillen et al. 1991; Green et al. 1984). In addition, Esfandiari and colleagues reported a marked improvement in VO_2max and CO during submaximal exercise secondary to increase in stroke volume and blood volume in response to short interval (60 sec at 95-100% VO_2max) training for 12 days with young healthy men (Esfandiari et al. 2014). In the current study, there was no measurement of blood volume in response to SIT. However, Green et. al demonstrated that exercise intensity is an essential determinant of elevated blood volume after supramaximal (120% VO_2max) short term interval training (3 days) with young healthy men (Green et al. 1984).

Short term SIT can be a potential exercise training for inducing plasma and blood volume expansion i.e., exercised induced hypervolemia as acute central adaptations. Further studies needed to assess the effect of SIT on blood volume in healthy population and COPD patients.

Blood pressure

Our results expanded the previous findings of reducing blood pressure in response to SIT (Whyte et al. 2010; Heiskanen et al. 2017; Holloway et al. 2018). In the current study, there was an improvement in resting SBP without changes in DBP. Nevertheless, there was a tendency of reduced DBP in the healthy group (figure 3). Conversely, in patients with fatty liver disease, SIT found to reduce DBP significantly without changes in SBP (Maclean et al. 2018). In a recent study with an elderly population, SIT for 10 weeks showed improved resting blood pressure (Adamson et al. 2018). However, the sprint duration in the latter study was only 6 seconds. To the best of knowledge, the current study is the first to report marked improvement of SBP in COPD patients and the elderly population after 3 weeks of interval training. However, moderate endurance training (38-65% PWR, 5 days/week) showed improvement in blood pressure associated with reduced arterial stiffness after 4 weeks with COPD patients (Vivodtzev et al. 2010).

The mechanism of reducing blood pressure with SIT is yet uncertain. A possible explanation for this reduction that SIT may induce parasympathetic activation through increased baroceptors sensitivity and vagal activity (parasympathetic drive) that can improve blood pressure (Fadel and Raven 2012). Another suggested mechanism for reducing blood pressure is the induced shear stress that can result from the vigorous intensity of SIT which can stimulate nitric oxide (NO) release and enhance endothelial function mediated through increased endothelial nitric oxide synthase (eNOS) which synthesize NO (Rakobowchuk et al. 2008; Cocks et al. 2013). On the other hand, HRR and resting HR i.e., markers of parasympathetic activation didn't change after SIT in the current study. Therefore, the potential induced shear stress from SIT may govern the improvement in blood pressure. Our finding supports the major role of training intensity to reduce blood pressure (Cornelissen and Smart 2013) in response to SIT with the elderly population and COPD patients.

Consequently, SIT can be a potential interval training method for reducing hypertension and arterial stiffness in patient populations and elderly individuals. On the other hand, there were no measurements of pulmonary blood pressure in the current study. Pulmonary hypertension is a common sign for COPD patients which needs invasive measurements to monitor. It can be an interest research area whether SIT can induce similar changes in pulmonary vascular resistance by reducing pulmonary artery hypertension in COPD. Further studies merited to

investigate the effect of SIT on pulmonary artery blood pressure and evaluate NO bioavailability after SIT.

Aerobic performance and muscle power

A major finding of the current study is the marked increase of aerobic performance during cycle TTE in COPD and healthy groups. In addition, there was a significant increase in peak exercise tolerance in terms of PWR in the healthy group and a tendency to increase in COPD group during maximal exercise. Moreover, there was a significant increase in anaerobic power through the increase in PPO during the training period of SIT (second to the last session) in both groups. In the COPD group, improvement in aerobic performance during TTE was possibly attributed to anaerobic power gained during SIT. In line with this, muscular adaptations are essential for the improvement in endurance performance in response to exercise training. These adaptations can be reflected by an increase in mitochondrial enzymes and decreased lactate production throughout the exercise (Bassett and Howley 2000). This can indicate that short term SIT in the current study have more peripheral adaptations with increasing muscle power and muscle oxidative capacity. Therefore, these peripheral adaptations may explain the marked improvement of aerobic performance during TTE with COPD and healthy group. On the other hand, a similar marked improvement of muscle power in the healthy group did not attribute to the improvement of aerobic performance during TTE. While in the healthy group, the dose of training is likely insufficient for a similar association. The small sample size can be a limitation for representing the training effect on both groups.

In agreement with our findings, Burgomaster et.al reported a marked increase in muscle oxidative capacity and mitochondrial activity after 2 weeks of SIT with young healthy individuals (Burgomaster et al. 2005). Interestingly, it has been demonstrated that SIT reduces anaerobic metabolism during intense exercise which in turn improve aerobic metabolism, and increase time to exhaustion favored to aerobic adaptations (Harmer et al. 2000). The measurement of mitochondrial enzymes and muscle oxidative capacity is beyond the scope of this study and was assigned to other colleagues in the same project.

Dissociation between cardiorespiratory function and aerobic performance

Our findings show a dissociation between cardiorespiratory function (SV, $\dot{Q}$, and VO_2) during work economy and maximal exercise, and aerobic performance during cycle TTE in both groups. In line with this, Chester et.al found similar dissociation between exercise tolerance (measured as energy expenditure) and central hemodynamics during walking (Chester et al. 1977). It has been suggested that dyspnea mitigation and improved walking efficiency can contribute to physical capacity improvement (Chester et al. 1977). Unlike our intervention, the pulmonary rehabilitation in the latter study involved four weeks of different physical training associated with chest physiotherapy and breathing exercises which can attribute to ventilation improvement during walking. Consistent with this, Porszasz et. al reported improvement in aerobic performance during TTE without changes of VO_2peak with COPD patients following continuous endurance training (75% of PWR) for 7 weeks. However, in the latter finding, the improvement in aerobic performance was attributed to ventilation improvement through reducing breathing frequency and dynamic hyperinflation contributed to this improvement (Porszasz et al. 2005). In the present study, there was a dramatic increase of TTE with the healthy group which can exclude the predominance of dyspnea mitigation in the improvement of aerobic performance with COPD patients. Nevertheless, neither dyspnea perception nor ventilation was measured during cycle TTE in the current study. Whereas, the ventilation was recorded during work economy and maximal exercise test show no changes after SIT (Table 2). It can be assumed that both groups in the current study are not used to cycling as a functional daily activity like walking. Thereby, a learning effect may contribute to the marked improvement of cycle TTE without changes in cardiorespiratory function during exercise.

Taken as a whole, there can be two possible explanation behind the disassociation of cardiorespiratory function and aerobic performance during TTE in the current study. The training dose (4 x 20 sec) and/or period (3 weeks) were not enough for improvement in cardiorespiratory function in both groups. Secondly, the severity of COPD and the natural history of the disease limits the physiological adaptation after short term SIT. In the current study, COPD patients were not classified whether hyperinflators or non-hyperinflators. In line with this, the nature of SIT is supramaximal intensity with all-out effort, those who have DH and aggravated by exercise may not attain the intensity required to induce cardiovascular and metabolic stress because of dynamic hyperinflation. It can be recommended to use bronchodilators before SIT to reduce the severity of dynamic hyperinflation and exertional

dyspnea which in turn reduce expiratory flow limitation during exercise (Thomas et al. 2013). Thus, COPD patients can gain additional physiological adaptation with attaining supramaximal intensity during SIT. Further studies merited to investigate using bronchodilators before SIT with COPD patients.

Limitations

The small sample size in the current study cannot represent different stages of COPD and training effect of SIT in elderly individuals. The reliability of impedance cardiograph during maximal exercise test is yet controversial. It has been demonstrated that it can overestimate CO compared to the Fick method because of lung hyperinflation (Bougault et al. 2005). On the other hand, in a very recent study impedance cardiograph showed validity against the dye dilution method during maximal exercise test with COPD patients (Louvaris et al. 2019). However, we did not have direct measures of CO to compare with our findings. Further studies needed to validate impedance cardiograph with invasive direct measurement of CO with COPD during intense exercise. Using cycle TTE as an assessment of aerobic performance with COPD patients can be a strength in the current study. It showed high sensitivity and reliability with training intervention in COPD patients (Oga et al. 2000). However, there were no measurements of SV, CO and VO_2 variables combined with cycle TTE which restrict the explanation of the marked improvement in performance during TTE. It can be recommended to perform cardiorespiratory measurements alongside with TTE or submaximal tests which reflects the functional capacity of the patients such as 6-minute walk test and/or cycle at 75% of PWR for 6 minutes. These examinations are feasible with COPD patients and resemble their daily living activities, may indicate the mechanism behind the improvement in aerobic performance in response to SIT (American Thoracic and American College of Chest 2003; Oga et al. 2000; Gloeckl et al. 2013). Further studies are needed to assess cardiorespiratory measurements during the aforementioned submaximal tests in response to SIT.

Participants were not asked to refrain from caffeine, alcohol, and smoking before baseline measurements which can overestimate blood pressure. However, it can be assumed that in 3 weeks their daily beverages intake did not change to a great extent that can confound the training effect. A possible strength in the current study that we measured blood pressure within 48-96 hours after the last training session to wash out the effect of post exercise induced hypotension which occur within 24 hours after exercise training.

Conclusion

The present study shows for the first time that 3 weeks of SIT can augment aerobic performance during TTE in COPD patients and healthy elderly individuals without improvement in cardiorespiratory function. In the current study, SIT was insufficient to induce central adaptations through SV and CO. Nevertheless, short-term SIT enhances peripheral vascular function through reduced SBP during rest which needs further investigations to examine direct measures of arterial stiffness and endothelial function in response to SIT with COPD patients. SIT is a feasible interval training with elderly individuals and can be implemented during pulmonary rehabilitation with COPD patients to improve functional capacity and exercise tolerance.

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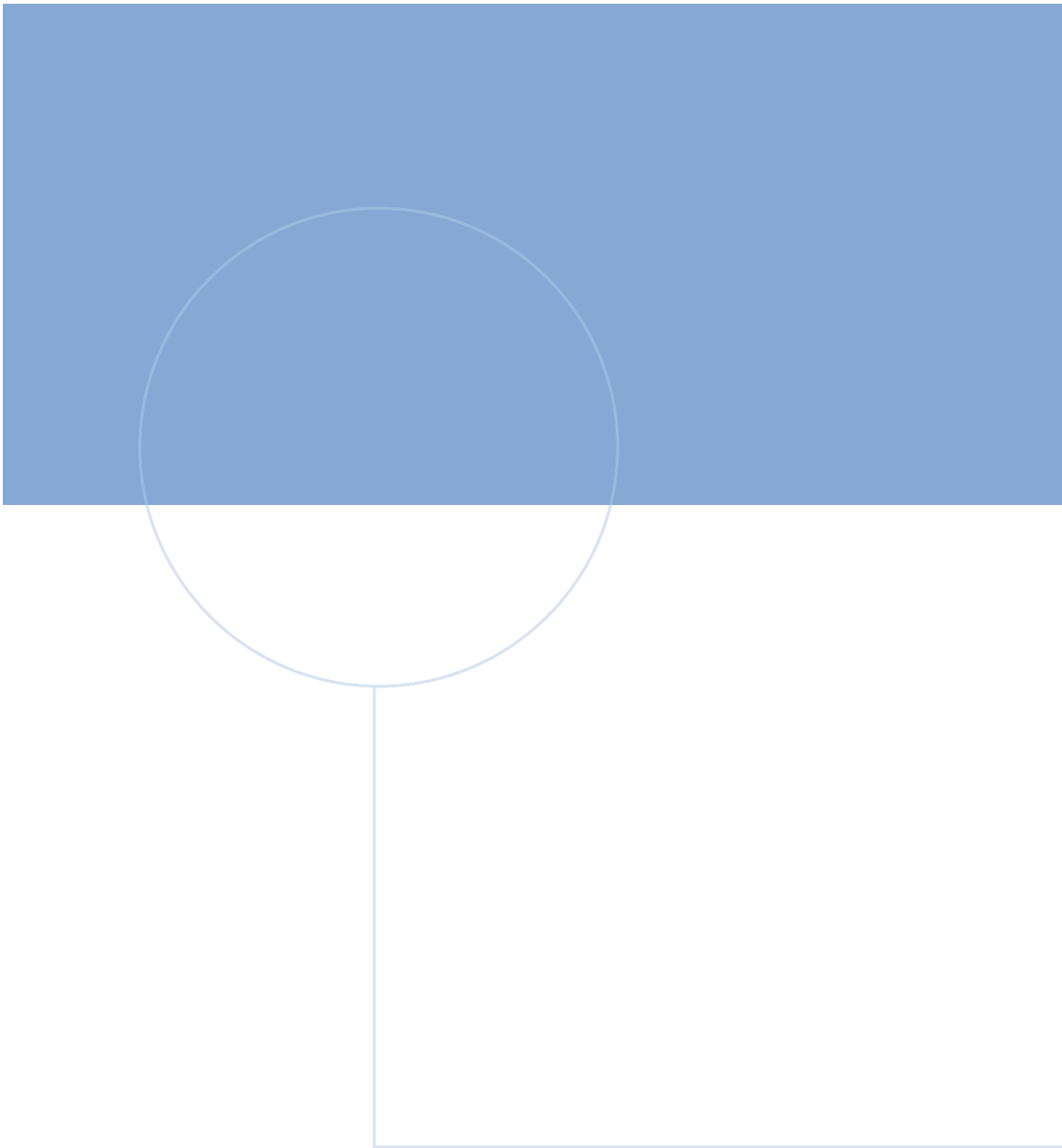

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