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Sprint Interval Training, a novel exercise modality to improve exercise tolerance in COPD and sedentary healthy adults and the role of microcirculation

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Abstract

Introduction: Chronic obstructive pulmonary disease (COPD) progression places a limitation on exercise capacity through the deterioration of lung function leading to a sedentary lifestyle, comorbidities and limited function. Exercise is undoubtably an integral part of rehabilitation to improve exercise tolerance, increase functional capacity, and decrease long term mortality risk. However, exercise is challenging in this patient population. Sprint interval training (SIT) has been widely studied, proving to be effective in increasing exercise performance, as well as aerobic capacity in individuals with lower baseline capacity. The effectiveness of SIT in COPD patients where skeletal muscle dysfunction is common has yet to be researched. SIT could prove to be time efficient and effective at improving exercise tolerance and/or aerobic capacity while avoiding the most prominent limitation to exercise COPD patients have, decreased lung function. The aim of this study was to study the microcirculation's role in SIT adaptations in COPD and healthy controls utilizing near infra-red spectroscopy.

Methods: 9 COPD patients and 8 healthy control subjects completed 3 weeks of SIT training. Training consisted of a 5min warm up, 4x:20s sprints, with 3-5mins of active recovery between sprints, 3xwk. HbO_2 slope from linear regression analysis on the first 15s after time to exhaustion (TTE) test was used to quantify microcirculation's ability to recover muscle tissue O_2 desaturation.

Results: Both COPD and healthy groups significantly improved TTE [3:47 ±3:59min (49%) (p=0.046), 5:42 ±4:28min (70%) (p=0.009)] respectively. COPD subjects did not improve VO_2peak while the healthy control tended to increase (p=0.089). No changes in HbO_2 recovery were found in the COPD group and healthy group [0.004 ±0.014 µM/s (p=0.44), -0.003 ±0.006 µM/s (p=0.28)] respectively.

Conclusion: Sprint interval training has proven to be effective at improving TTE, a common measure used to judge the efficacy of pulmonary rehabilitation on exercise tolerance. Improvements in microcirculation function were not detected. Regardless, just 12 minutes of supramaximal exercise divided into 36 sprints over 3 weeks could be a useful "kickstart" to pulmonary rehab, allowing subsequent training to be at a higher relative intensity which is more effective and time efficient at improving VO_2peak and functional capacity.

Foreword

This Master's Thesis is a piece of a study completed as a team with two other students. We all worked to complete the study but also had our own measurements we were responsible for to use in our own respective thesis. One member of the team worked with biopsies for mitochondrial respiration data, another utilized a PhysioFlow device to observe any central cardiovascular adaptations that may occur, and I utilized Near Infra-red Spectroscopy to record possible changes in muscle microcirculation and O_2 consumption. In this fashion, we aimed to observe what adaptations to training are occurring and which are the most responsible for the possible improvement in exercise capacity shown by the subjects. This design also allows for more discussion on which factors adapt to training the most in the different groups and why. The data would be pooled for possible publications.

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Abbreviations

Chronic Obstructive Pulmonary Disease
    COPD
Cardiopulmonary exercise testing
    CPET
Respiratory Exchange Ratio
    RER
Sprint interval training
    SIT
High intensity Interval Training
    HIIT
Moderate Intensity Continuous Training
    MCIT
Revolutions per minute
    RPM
Heart Rate
    HR
Blood Lactate
    $[La^-]_b$
Peripheral capillary oxygen saturation
    SpO_2
Stroke volume
    SV
Lactate Threshold
    LT
Motor Unit
    MU
Global Initiative for COPD
    GOLD
American Thoracic Society
    ATS
European Respiratory Society

ERS
Activities of Daily Living
    ADL's
Body Mass Index
    BMI
Cardiac Output
    CO
Near Infra-red Spectroscopy
    NIRS
Work Economy
    C
Treadmill Work Economy
    TWE
Cycle Work Economy
    CWE
Time to exhaustion
    TTE
Peak work rate obtained in VO$_2$peak test
    WRpeak
Total Hemoglobin
    tHb
Oxyhemoglobin
    HbO_2
Tissue saturation index
    TSI
Adenosine Triphosphate
    ATP
Phosphocreatine
    PCr
Peak Power Output during Wingate
    PPO

Introduction

Exercise is an important factor in maintaining long term health and physical function.[1-3] Using exercise as medicine has slowly gained traction as researchers have amassed data for several decades.[4] Those affected by chronic obstructive pulmonary disease (COPD), tend to have especially low exercise capacity [5] which subjects them to a lifestyle that only further deteriorates their health. Whether caused by the primary disease, or a by-product of their lifestyle, exercise intolerance makes exercise to improve their health and function challenging. The ability to exercise at higher intensities, as recommended to the general population [6], is not feasible for many affected by this disease. Current alternatives like single leg cycling are more effective [7] yet more time consuming. In a search to find alternatives, my colleagues and I tested the efficacy of sprint interval training in this disease population with the notion that very short bursts of intense exercise can side step their primary limitation, ventilation, while providing a strong stimulus for improvements at the local muscular level. Our idea was to use SIT to provide a "kickstart" to the peripheral muscle and allow subsequent training to be completed at a higher relative intensity, therefore providing a stronger stimulus for adaptations and improvements in health and functional capacity.

Aerobic Exercise Performance and Health Status

What can be considered aerobic exercise is highly relative and depends on an individual's maximal capacity for work. For top athletes, intensive aerobic exercise can be pushing the physiological limits of what humans can accomplish. In very old or patient populations, intensive aerobic exercise is often climbing stairs or even daily tasks.[3] Nevertheless, aerobic exercise performance is determined by a combination of maximum aerobic power (VO_2max), work economy (C), and lactate threshold (LT).[8-11]

Maximum Aerobic Power

Cardiorespiratory fitness (CRF) describes the maximal amount of oxygen an individual can uptake and utilize for work.[12] During incremental cardiopulmonary exercise testing (CPET), oxygen uptake increases with each increase of work. CPET ends when subjects display a plateau of O_2 uptake regardless of increases in work or the subject ends the test due to exhaustion. O_2 uptake does not always plateau before the subject ends the test from exhaustion.[12-14] When a plateau is observed despite increasing workloads, the VO_2 measurement can be called maximal (VO_2max).[12] When no plateau is observed, the highest

level reached is denoted as VO_2peak.[13] For simplicity, in this thesis, all maximal CPET test results will be termed VO_2peak.

VO_2peak is a paramount variable for exercise performance and health.[1-3, 8, 15-17] For athletes VO_2peak is the single most important factor determining success in performances lasting longer than several minutes.[8, 15-17] On the other end of the spectrum, patient populations can have a VO_2peak so low that it limits their performance in activities of daily living (ADL) like walking and stair climbing.[3, 18] VO_2peak, used to quantify CRF, has well known significance in long term health.[1-3]. When observing health outcomes in men referred for exercise testing, Myers et al. concluded that VO_2peak was the most powerful predictor of an increased risk of death among normal and cardiovascular disease subjects. Furthermore, increases in VO_2peak of 1 metabolic equivalent (MET) ($3.5 \text{mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) [13] in treadmill performance was associated with a 12% improvement in survival.[1] Having a high age specific VO_2peak reduces the negative effects of increased sedentary time on cardiovascular risk factor clustering regardless of the compliancy to recommended weekly activities.[2] The importance of VO_2peak in performance and health cannot be overstated.

Factors Limiting VO_2peak

VO_2peak is a very complex variable in exercise performance due to the entwined and deeply integrated bodily systems that work together to accomplish O_2 consumption.[14] O_2 consumption starts with lung ventilation that fills alveoli with atmospheric air. O_2 is absorbed while CO_2 is simultaneously eliminated from the blood stream. This movement of gases occurs due to diffusive forces caused by unequal partial pressures. In the case of O_2, transport is assisted by forming reversible bonds with heme molecules found in erythrocytes. The heart works as the pump to deliver the oxyhemoglobin through the arteries and capillaries to the oxygen consuming cells.[17, 19] Due to consumption of the O_2, metabolically active tissue has a lower partial pressure of O_2 (PO_2) than the blood supplying it.[20] This reverses the bonds to heme and releases O_2 which diffuses into the mitochondria to be utilized in oxidative phosphorylation to produce ATP. Any step in the process, and variables that can affect the steps, has the potential to limit VO_2peak.[14, 21]

Debates and discussions on what limits VO_2peak have further demonstrated the complexity. Much of the credit for the development of the concept of VO_2peak has been given to Archibald Hill. Hill and contributors concluded that much of the individual differences in

VO$_2$peak were due to differences in cardiac output.[12] This was based on the Fick Equation (VO$_2$ = Cardiac Output x arteriovenous oxygen difference), measured VO$_2$, and assumed O$_2$ content of arterial and mixed venous blood during exercise. Since Hill's time this subject has been visited several times over. Noakes considered the fact that a plateau is not always seen to be proof that cardiac output was not the limitation, rather muscular factors signaled a "central governor" to protect the body from hypoxia and limited VO$_2$peak.[22] Basset and Howley rebutted the notion pointing out that the plateau is not the principle evidence of the widely accepted cardiopulmonary limitation.[23] The plateau simply represents that oxidative phosphorylation has reached maximum ATP generation regardless of what limits it.[14]

Supply or Demand Limitations

With disagreement driving debate, it became clear: supply of O$_2$ or demand of O$_2$ can be limiters.[14, 21, 24] Relating to the Fick Equation; supply embodies oxygen uptake and delivery, mostly dictated by cardiac output (CO), and demand embodies arteriovenous oxygen difference (A-VO$_2$ difference). The supply/demand theory of VO$_2$peak limitations have been discussed in detail.[12, 14, 16, 21-23]

CO quantifies the ability of the heart to pump blood into the arterial supply system and is measured in (L· min^{-1}). CO is a product of stroke volume (SV) and max heart rate (HRmax). SV is the amount of blood ejected from the heart after a single contraction and is influenced by the size of the left ventricle, the contractility of the ventricle, venous return, and plasma volume.[25] Since HRmax cannot be increased with exercise [26], adaptations to improve supply are solely attributed to increases in SV in both young and old subjects.[6, 21, 27, 28] A-VO$_2$ difference reflects the ability of muscles to extract O$_2$ from arterial supply. This is measured by computing the difference between the O$_2$ content of venous return from a muscle group and the O$_2$ content of arterial supply to the same muscle group.[29] A-VO$_2$ difference relies heavily on mitochondrial content and microcirculation indices of muscle being measured.[30] Mitochondrial size, density within muscle, and efficiency all affect how much O$_2$ muscles can accept and utilize for ATP generation. Microcirculation can be quantified in many ways including, but not limited to: number of capillaries around a fiber (Ncaf), capillary to fiber ratio(C/F$_i$) and simply capillaries/mm^2 of muscle.[31, 32] The size of capillary to fiber interface can be estimated from the quotient of the C/F$_i$ and fiber perimeter for each fiber (CFPE

index).[33] All factors and variables included in A-VO$_2$ difference are different between muscle fiber types and are mercurial.[31-34]

Vascularization, in terms of C/F$_i$ and capillary/mm^2, increasing as a result of training suggests that it may be a limiter in VO$_2$peak.[32, 35] Improvements in vascularization increases blood flow as well as decreases diffusion distance to mitochondria.[32, 35] Mitochondrial density and function has been shown to increase post training as well.[35-37] In theory these adaptations would make significant increases in VO$_2$peak. This has not been the case; studies have shown several times increase in mitochondrial activity or density only corresponding to modest increases in VO$_2$peak.[34-36] Increased vascularization does not correlate well with increased VO$_2$peak either.[32, 35] This suggest O$_2$ demand and peripheral factors are not limiters.

Demand limitations seemed more likely when Saltin et al. demonstrated that exercising one leg increases VO$_2$peak of that leg more than the non-exercising leg.[38] In the contrary, Clausen et al. presented evidence that cardiac output adaptations are responsible for increases in VO$_2$peak by demonstrating leg exercises can increase VO$_2$peak in arm exercises.[39] Saltin and collaborators then conducted another study measuring O$_2$ uptake and blood flow during single leg and whole body exercise.[29] O$_2$ utilization and blood flow was several times higher during single leg exercise than during whole body exercise. Saltin et al. concluded that during whole body work, the muscles can utilize more O$_2$ than the cardiovascular system could supply.[29] The idea that supply of O$_2$ is the limiting factor rather than the demand of O$_2$ at the muscular level in healthy subjects during whole body exercise at sea level has since been solidified by many studies.[12, 16, 29, 39-41]

When looking at very sedentary subjects or patient populations, it seems that their ability to supply O$_2$ does not limit their VO$_2$peak, rather they have a demand limitation.[14, 28] More specifically, their VO$_2$peak is limited by the extraction and utilization of O$_2$ by the muscle. This could be due to decreased indices of microcirculation and/or mitochondria depending on the disease state. Demand limitations are revealed when supplying supplemental O$_2$ does not improve VO$_2$peak and decreasing O$_2$ supply does not decrease VO$_2$peak.[14] Instead of the changes in O$_2$ supply, the muscles ability to utilize the supply is the bottle neck. Of course, with sufficient hypoxia anyone and everyone will see decrements in VO$_2$peak.

Work Economy (C) is referred to as the ratio between work output and VO_2.[8, 16] C is commonly quantified as the VO_2 ($mL \cdot kg^{-1} \cdot min^{-1}$) at a standard velocity ($m \cdot min^{-1}$). Therefore, C expresses the cost of O_2, to perform at a given velocity. If you convert VO_2 and work rate to ($kcal \cdot min^{-1}$) you can divide the work accomplished by the energy expenditure and multiply by 100 to get a work efficiency percentage. Work efficiency expresses the percentage of the total energy expenditure that was actually used for work.[42] Healthy individuals typically have 25% efficiency, meaning that of all the energy consumed during work only 25% was actually used for work, the rest wasted as heat production.[43] In elderly and patient populations, work efficiency tends to decrease which can significantly decrease their performance.[31, 42, 43]

It is beneficial to performance at any level that C is as low as possible.[8, 9, 42, 44] Improvements in C means the same work load pre-training requires less O_2 post-training.[44] C can be a defining factor in distance races in which participants have similar VO_2peak.[44, 45] Decreases in energy demands for a workload due to improvements in C can also increase time to exhaustion (TTE), an important index in performance for athletes and patient populations.[9, 46]

C is influenced by many factors. A major factor defining C and work efficiency in all individuals is muscle fiber type. Muscle fiber types were originally classified into two distinctions, type I and type II. Type I fibers have more mitochondria and higher microcirculation indices. They use oxygen much more efficiently while resisting fatigue. Type II fibers are known to be heavy lifters, being able to produce much more force. Type II fibers have much fewer mitochondria with less capillarization and are therefore less efficient with O_2 use.[19] Though there are clear distinctions between the opposite sides of the spectrum, muscle fibers are mercurial and can shift in both direction of the spectrum depending on training modalities.[19] Mitochondrial efficiency can decrease with age which can also affect C especially in elderly and patients.[47]

Type I fibers have smaller motor units (MU) than type II fibers.[48] The Henneman's size principle describes the phenomenon that during activity, MUs are recruited preferentially, starting with the smaller and weaker and moving up to larger and stronger MUs as needed.[49] In this way, muscular strength plays an important role in C. For the most efficiency in an activity, it would be preferential to recruit the least amount of muscle mass to complete a task.[50] Those who have a higher muscular strength find the same workload relatively easier

and therefore recruit fewer, smaller MUs.[51] Neuromuscular factors like motor control and less co-contraction of antagonist can play a role in C, especially in elderly and patients.[31]

Lactate Threshold

LT is the highest work rate, as defined by %VO_2max or %HRmax, using large muscle groups in which lactate production and elimination are balanced.[45] Anaerobic metabolism begins to play a part of energy production when PO_2 decreases. The long-lived belief that inadequate muscular oxygenation during incremental exercise initiated anaerobic energy production [12] has since been challenged. It seems that systemic, not intracellular, decreases in PO_2 increases catecholamine response during exercise which is closely related to muscle lactate efflux.[52] Lactate, the byproduct of anaerobic metabolism, is highly associated with acidosis.[53] Lactate can be circulated and used for energy elsewhere like cardiac or ventilatory muscles.[17] However Lactate influx, and subsequent decreases in pH, decreases the muscles' ability to contract and function to full capacity.[54] LT is therefore the highest relative workload an individual can maintain for extended periods of time.[8] Intensity above LT correlates negatively with how much time can be spent working at that intensity.[16, 17] This concept is termed fractional utilization of VO_2max. Athletes may be able to work around 87% VO_2max for an hour but at 83% for 2, and even less for 3 hours.[17] The fractional utilization for the average healthy person would typically be less but varies depending on muscle fiber type, training status, and genetics.

What determines an individual's LT has been a topic of much debate with the precise answer remaining elusive. When studying the relationship between the respiratory capacity of an individual's skeletal muscle and LT, Ivy et al. found that the maximal capacity of muscle tissue to oxidize pyruvate was strongly correlated with LT, both at an absolute measurement of work and %VO_2max. In the same study, proportion of type I fibers were also closely related to absolute and relative LT.[55] This seems to fit the idea that decreases in PO_2 initiates lactate efflux as type I fibers are more efficient with O_2.

Chronic Obstructive Pulmonary Disease

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) defines COPD as "a common, preventable, and treatable disease 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."[56] The most well known risk factor is smoking but even in heavy smokers, <50% develop COPD in their life time.[57] Nevertheless

smokers tend to develop into the more severe stages, have a higher burden of systemic inflammation, and have more symptoms.[58] Other environmental factors include: environmental tobacco smoke, organic and inorganic dust, chemicals, fumes, biomass smoke, animal feces, and coal residue. Lung or airway infections, especially during childhood, asthma, airway hyperreactivity, and genetics are all risk factors that are found to increase susceptibility.[59]

COPD is an umbrella term encompassing several respiratory conditions that can often overlap. Chronic bronchitis, emphysema, and refractory asthma are the most prominent of the conditions encompassed in COPD.[60] Chronic inflammation causes structural changes, small airway narrowing, and destruction of lung alveoli; the ends of the bronchial tree responsible for gas transfer with blood.[56, 61, 62] These developments can decrease the lungs elastic properties, enlarge the lungs [63], obstruct airways [61], damage cilia and decrease their ability to move mucus up and out of the airways [62], and decrease the lungs diffusive properties [64]; all of which negatively impact overall lung function. [56, 61-64]

Diagnosis of COPD requires spirometry tests to measure airflow limitations.[59] The FEV1/FVC ratio is a calculated ratio of the proportion of a person's vital capacity that they can expire in the first second of forced expiration (FEV1) to the full, forced vital capacity (FVC). The current GOLD definition for airflow limitation is an FEV1:FVC ratio of less than 70% of the predicted value, measured with post-bronchodilator lung function. COPD diagnosis is further classified into four stages (Mild, Moderate, Severe, Very Severe) from the FEV1:FVC value as a way to generalize the severity of airflow limitation.[59, 65]

COPD is the third leading cause of chronic morbidity and mortality in the United States.[66] In 2015 alone there were about 3.2 million deaths from COPD [67] and this is likely an underestimate due to the high prevalence of comorbidities and underreporting on death certificates.[68, 69] Adeloye et al. reports a global prevalence estimate of 11.7% (95% confidence interval 8.4%– 15.0%).[70] With the aging populations of high income countries and increased incidence of smoking in developing countries; COPD prevalence is expected to increase over the next 30 years with 4.5 million deaths annually to be expected in 2030.[59, 71]

While spirometry is essential for diagnosis, evidence shows that there are other important factors predicting both quality of life and survival of patients with COPD.[72] Some of these factors include: functional status [73-75], respiratory symptoms other than cough or sputum [76],

fat-free body mass [77-81] exercise capacity [1, 4, 7, 42, 59, 82-89], and the presence of comorbid diseases, such as depression, heart failure, and cancer. [68, 90-92]. COPD subjects are plagued by comorbidities related to their lifestyle which includes exposure to similar risk factors and sedentary behavior. COPD is a lifestyle related disease that further perpetuates a sedentary lifestyle due to exercise intolerance which continues to deteriorate health while increasing the individual's susceptibility to other lifestyle related diseases.[59, 85, 92-94]

Treatment

According to GOLD the main outcomes to treatment of stable COPD are to: reduce symptoms, improve exercise tolerance and health status, prevent disease progression, and reduce the risk of future exacerbations and mortality.[59] First and foremost on all treatment plans is smoking cessation and/or eliminating risk factor exposures.[59, 65] Pharmacological therapy varies depending on the underlying causes, comorbidities, and prominent symptoms of each patient and can be effective at reducing symptoms, improving health status and exercise tolerance, and reducing risk and severity of future exacerbations.[59] Pulmonary rehabilitation improves symptoms, quality of life, and participation in daily activities.[59] As defined by ATS/ERS: "Pulmonary rehabilitation is a comprehensive intervention based on a thorough patient assessment followed by patient tailored therapies that include, but are not limited to, exercise training, education, and behavior change, designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence to health-enhancing behaviors".[95] Among all therapies, the most relevant to this thesis is exercise.

Physiological Consequences of COPD

Exercise intolerance is ubiquitous and complicated in COPD patients. Exercise intolerance is multifactorial stemming from ventilatory, cardiovascular, metabolic, and locomotor muscular systems in highly variable combinations.[43, 84, 85, 94, 95] Clearly, breathing limitations have always been a concern when evaluating exercise intolerance in COPD patients. Ventilatory requirements during exercise are higher in COPD than healthy controls due to increased work of breathing, increased "dead space", and impaired gas exchange.[46, 61-63, 95-98] Individuals with COPD have limited maximal ventilation during exercise due to the expiratory flow limitation which increases end expiratory lung volume (EELV) despite no changes in total lung volume.[96, 97] The temporary increase in EELV when ventilation is increased is termed dynamic pulmonary hyperinflation. Dynamic hyperinflation significantly

increases the work of breathing, especially because the ventilatory muscles are put into a mechanical disadvantage.[96, 97] All of these factors decrease the ability of the lungs to supply blood with O_2 and increase the demand of O_2 to ventilatory muscles which can limit the supply to locomotion muscles. (supply limitation)

In 1992, Killian and collaborators [98] reported that leg discomfort was a recurrent exercise limiting symptom in COPD patients during a standardized cycling protocol. This report has become the foundation of a thriving research topic; lower limb dysfunction is a major factor in exercise intolerance in COPD patients, hinting at demand limitations. Peripheral muscle's functional capacity is determined by its strength and endurance. Hamilton and collaborators [51] showed that compared to healthy subjects, patients with respiratory failure, heart failure, or a combination had significantly less strength in peripheral muscle which was strongly related to their lower maximal work capacity on a cycle ergometer. Muscular strength was also associated with decreased symptoms of intensity at any given power output for healthy and patients groups suggesting that muscular strength is related to exercise tolerance.[51] The striking similarities in muscular alteration underlying the exercise impairment in COPD and chronic heart failure also suggests that the sedentary lifestyle induced by the diseased state contributes to exercise intolerance.[94] Muscular atrophy, mitochondrial dysfunction, poor oxidative capacity, and a shift in fiber type are all possible contributing factors in the deterioration of peripheral muscle functional capacity.[59, 80, 84, 85, 94, 99-103]

The prevalence of underweight (according to World Health Organization criteria) in COPD increases with disease severity, up to 30% in patients with GOLD stage 4.[80] This is only in reference to body mass index (BMI) and doesn't take into account fat free mass index (FFMI). FFMI can be used instead to highlight the impact of atrophy and cachexia on this population. FFMI express the same increased prevalence with disease progression with 50% of GOLD stage 4 being below the 10th percentile of FFMI in general population. FFMI was also a strong predictor of mortality.[80, 81] To make the situation worse, remaining skeletal muscle tends to shift towards the less efficient type II fibers contradictory to the normal aging fiber type shift.[99, 101, 102] Inefficient type II fibers, as well as weakness which affects sustainable work rate and exercise tolerance [51], are certainly part of the equation of COPD exercise intolerance.

Mitochondrial function is altered in the muscle tissue of COPD patients, decreasing locomotor muscle oxidative capacity.[100, 104, 105] It is difficult to determine whether these

abnormalities are a result of a myopathic process specific to COPD or the result of the muscle inactivity in this population.[84, 94, 95, 105] When compared with healthy control subjects, mitochondrial density and mitochondrial function are reduced in the lower limb muscle of patients with COPD.[100, 104, 105] Muscle fiber type shift, mitochondrial density/function attenuation, and muscular weakness in COPD patients are causes of the low mechanical efficiency displayed by this patient group.[42, 104, 106]

Research in capillarization of skeletal muscle in COPD patients have seen conflicting results.[84] Some studies have observed lower capillary density and number of capillaries per muscle fiber in skeletal muscle.[101, 103] Others have failed to show a statistical difference[106], while some find that correcting for cross sectional area of muscle makes capillarization indices similar to healthy subjects.[103, 107] Eliason and collaborators [107] utilized muscle-to-capillary interface (CFPE-index) which has been suggested to be a more sensitive marker for changes in the capillary bed compared to the previously mentioned indices.[108, 109] They found that CFPE-index in COPD was attenuated with correlations between CFPE-index, disease severity, and exercise capacity.[107]

For healthy individuals during whole body exercise; local muscle's ability to consume O_2 surpasses the ability of the cardiovascular system to supply O_2. Muscle fiber type shift, along with mitochondrial and microcirculation declines can decrease local muscle's ability to extract and consume O_2 to the point that it no longer exceeds the ability of the heart to supply O_2. As described by Gosker and Maltais [85, 94], there is an evident downward spiral of dysfunction. The primary disease symptoms of expiratory flow limitations and dynamic hyperinflation provide a barrier to exercise and submit the affected to a more sedentary lifestyle. The sedentary lifestyle induces negative cardiovascular and muscular adaptations which further increase exercise intolerance and further decrease health status. Exercise as the cornerstone of pulmonary rehabilitation helps to improve exercise tolerance, improve health status, and encourage a more active lifestyle which encompasses the goals for treatment set by GOLD.[59, 83, 95]

Exercise and COPD

When discussing aerobic training, the "dose" of exercise prescription is expressed as frequency, duration, and intensity of exercise.[110, 111] Intensity and duration classify training into different modalities while frequency can vary no matter what modality is used. Frequency as

low as once a week can result in improvements for unfit subjects. As subjects get more fit, especially as VO_2peak surpasses 50 mL $\cdot$ kg^{-1} $\cdot$ min^{-1} , at least 3x a week is needed.[110]

Two widely researched aerobic exercise modalities are moderate intensity continuous training (MICT), and high intensity interval training (HIIT). As evident in the names, they vary in intensity, as defined by percentage of HRmax. High intensity interval training (HIIT) is defined as aerobic activity that works at high intensity which requires active rest periods to recover from such intense work.[6] While HIIT can have varying protocols, the most common protocol involves working at 90-95% HRmax during 4x4 min intervals and 60-75% HRmax during active rest.[6, 112, 113] MICT is characterized by any aerobic exercise at a maintainable intensity below LT for extended periods of time. MICT is typically long distance or volume training at 50-70% of HRmax.[6, 30, 112]

Previously it was believed that these variables that characterize training modalities are interchangeable. For example, decreasing one variable like intensity can still improve VO_2peak by increasing another like duration.[110, 111, 114] This notion of interchangeability has since been disproven.[6, 110, 112, 113, 115]. Because healthy individuals are mostly supply limited [40], SV changes are the main culprit of improved VO_2max.[6, 21, 27, 28] It is more effective and time efficient to train at higher intensities because SV may increase with increasing intensities, even up to maximal efforts for trained individuals [116]. Even for those who plateau in SV at submaximal intensities, the higher strain on the cardiovascular system challenges the heart more and provides a stronger stimulus for adaptation. For increasing SV and therefore VO_2max, HIIT is superior to MICT despite less volume because intensity cannot be substituted with volume.[6]

The concept of intensity over duration creating a more potent stimulus for adaptations is expressed when observing peripheral adaptations as well. Mitochondria indices tend to improve more from higher intensities. While mitochondrial improvements do not have such an astounding impact on VO_2peak for supply limited individuals, those who are demand limited may benefit vastly from these peripheral improvements. When comparing continuous protocols ($\approx$36min at 80% VO_2peak vs. $\approx$70min at 39% VO_2peak), higher intensity training phosphorylated mitochondrial biogenesis signaling proteins to a greater extent than lower intensity.[37] In a review on the role of intensity on adaptations, MacInnis et al covered many studies comparing

intensity and mitochondrial indices improvements and came to the conclusion that higher intensity mediates larger mitochondrial response.[30]

While HIIT is certainly the most effective training, it is not feasible in COPD patient. Work at such high intensity will cause dynamic hyperinflation for most of the patient population. Richardson et al. displayed an eloquent technique to avoid the limitations of high intensity while still reaping the benefit; one legged cycling.[117] This type of training avoids the ventilatory limitation as less muscle mass is working which requires less O_2. At the same time, exercise intensity at the muscular level is not compromised. Bjørgen et. al. furthered this concept by comparing the effectiveness one and two-legged 4x4min HIIT cycling protocols in COPD patients. While both groups improve VO2peak and WRpeak, the one-legged cycling group improved significantly more.[7] While this modality of training has been effective, major associations (ATS/ERS, AACVPR, ACSM) keep their recommendations on the simplistic side. Higher intensity (60-80% WRpeak) walking or cycling for 20-60min per session, 3-5 days/week.[83]

Effects of SIT in Healthy Populations

Sprint interval training (SIT) is a low volume form of HIIT that involves short burst of supramaximal work. Protocols vary but are generally described as supramaximal efforts of 10-30s, repeated 3-10x with several minutes for recovery.[30] SIT has been demonstrated to be as effective as MICT at improving VO2max despite the significant decrease in volume and duration.[118-123] In a meta-analysis of 19 studies, Sloth et al. found an average VO2peak increase of 4.2–13.4%.[124] The efficiency of SIT is a great benefit but spending more time in high intensity exercise like classical HIIT seems to stand as the most effective protocol for improving VO2peak.[6, 121] This claim is strengthened by the apparent plateau of SIT effectiveness when subjects are around (50 mL · kg^{-1} · min^{-1}) as cardiovascular O_2 delivery is certainly the limiting factor.[123]

Because SIT training is supramaximal, the adjustable variable in SIT to improve VO2peak appears to be rest periods. Bogdanis et al. demonstrates that ≤3.8mins of rest restricts complete phosphocreatine (PCr) re-synthetization between sprints. Without complete restoration of PCr, the second sprint caused a drop in PCr levels equal to post first sprint levels in just 10s rather than 30s. Aerobic metabolism was responsible for up to ≈50% of the total energy production in the second sprint.[125] This could explain some of the effects of SIT on aerobic

function and why Liljedahl et al., who included a 20-min rest between bouts, found no changes in citrate synthase, a marker of mitochondrial function.[126] The degree of the work:rest ratio seems to be of the upmost importance for the aerobic gains observed after SIT.

Effects on Cardiac Output

Very few studies with SIT as the intervention show improvements in CO. The most notable is a study with obese female subjects that improve SV by 11% during submaximal cycling while improving VO_2peak by $\approx$13%. The likely cause for such improvements is the low pretraining VO_2peak levels (21.6 ± 1.1 mL $\cdot$ kg^{-1} $\cdot$ min^{-1}).[127] It is well known that subjects with lower VO_2peak values show the highest improvement potential.[17, 19] Åstrand and Rodahl suggests adaptations to CO require sufficient time at high intensities so that SV matches the workload demand. This adjustment period of 1-2 minutes would certainly explain the lack of CO improvement findings in SIT literature as stroke volume likely doesn't match the workload during the sprint.[17]

Effects on A-VO$_2$ Difference

As discussed, active rest periods can be manipulated so that local muscle oxidative metabolism recovering the energy deficit can be challenged to provide beneficial adaptation. In just two weeks ($\approx$15min intense exercise not including warm up and cool down), recreationally active men increased the mitochondrial density marker citrate synthase activity by 38%.[128] No changes in VO_2peak were seen, as expected, due to the lack of demand limitations in this group (VO_2peak = 45 ± 3mL $\cdot$ kg^{-1} $\cdot$ min^{-1}) Even when supply is the limitation of VO_2peak, these subjects still benefitted from increased mitochondrial function with a 100% increase in cycling endurance capacity.[128] Gillen et al. found almost 2x the improvement in citrate synthase activity (48% vs 27%) from inactive men when comparing SIT and MICT after 12 weeks of training.[122] This is despite a five-fold decrease in volume and time commitment providing more evidence that intensity is an imperative variable in mitochondrial adaptations. In contrast, Gibala et al. found no statistical difference in mitochondrial oxidative capacity when comparing SIT and MICT, but the 90% decrease in training volume between the two modalities still displays intensity's effect on mitochondrial adaptations.[129]

Even in endurance trained males, decreasing training from 45km/week of MICT to just 5.7km/week of SIT maintained citrate synthase activity and C/F_i.[123] However, intensity does not seem to dictate microcirculation adaptations.[120] Shear stress on the luminal wall of blood vessels is necessary for angiogenesis. SIT provides a limited time of high shear stress and less

aerobic energy turnover than MICT which is closely linked to capillary density. Gliemann and collaborators state that, "the stimuli for capillary growth of anaerobic all-out efforts are naturally limited".[130] Increases in microcirculation beyond other training modalities does not seem likely with SIT for the average healthy populations.

Muscle Fiber Types

Adaptations to muscle fiber type during SIT are likely related to the high level of fiber recruitment that occurs during an all-out bout. The ability of SIT to stress the type II muscle fibers is thought to be an important influence for oxidative capacity improvements.[124, 126, 129, 131] According to Henneman's size principle, MICT would recruit predominantly type I fibers and cause adaptation to those fibers.[49] When the highest threshold fibers are activated and challenged aerobically they can shift to have more oxidative characteristics.[132] Bailey et al. demonstrated that SIT elicited greater oxidative enzyme adaptations in type II fibers than MICT. Furthermore, when exercise intensity is above VO_2peak, type IIx fibers, the least O_2 efficient fibers, improve oxidative capacity.[133]

How SIT could impact COPD patients

The capacity for SIT to improve VO_2peak and/or CO is limited to those with lower aerobic fitness.[123, 127] Since the majority of COPD patients fall into the lowest category of aerobic fitness [5], the idea that SIT can improve VO_2peak or CO is not improbable. The importance of improving VO_2peak cannot be understated as it is a powerful predictor of long-term mortality in healthy and disease populations.[1-3] Improving cardiovascular health could also help with decreasing the risk of comorbidities which plagues this patient group.[2, 85] SIT could have big implications for exercise performance in terms of ability to complete ADLs and independence in old age.[3] Any increases in VO_2peak means that ADLs are relatively easier [3] due to the fractional utilization of VO_2peak principle.[16, 18] It is safe to assume patients who increase VO_2peak have increased abilities to complete ADLs; or possibly more intense, HIIT to get the most potent stimulus for further central adaptations.[6, 121]

SIT is clearly a strong stimulant for peripheral muscle adaptations [30, 118-122, 128, 134] which could be instrumental for exercise tolerance improvements in COPD patients.[84, 100-103] Time to exhaustion (TTE) tests have been used regularly to assess the effectiveness of interventions on exercise tolerance in COPD.[46, 85, 95] The mitochondrial adaptations seen by Burgomaster in healthy subjects after SIT have corresponded to 100% TTE improvements with no changes in VO_2peak.[128] Even if SIT has little to no effect on VO_2peak, exercise tolerance

could still improve through peripheral factors. While microcirculation improvements are more ambiguous[85, 120], intensity is certainly the most potent stimulus in mitochondrial improvements[35, 37, 128], especially starting from a low fitness level[122].

The sedentary lifestyle, disuse of muscle, and hypoxia causes muscle fiber to transition to type II fibers which can reduce work efficiency.[94] SIT's ability to activate MUs up to the higher threshold type II fibers, and transition them to more aerobic characteristics is an important variable when considering performance improvements.[124, 131, 133] The peripheral improvements: mitochondrial function/density, microcirculation indices, and fiber type transition can have impactful effects on TTE, exercise tolerance, and recovery after intense work.[122, 128] Furthermore, just 2 weeks of SIT has been shown to improve PCr recovery post moderate intensity exercise [135] which can directly translate to less time resting after ADLs like extended walks or stair climbing.

To my knowledge, SIT has never been studied in COPD patient groups. The concept that SIT can be adapted for clinical settings[136], and can provide the powerful peripheral muscle stimulus without the limitation of ventilation is certainly questionable. The sprints are predominantly anaerobic and the O_2 debt created by the sprint can be paid off in the active recovery. In this way, the COPD patients can take time to reduce the breathing strain created by the O_2 debt before the start of the next sprint. It is possible that more severe stages of COPD may require too much time between sprints to return breathing to suitable levels and avoid dynamic hyperinflation. Too much rest may prove to be detrimental to the effects of SIT. This has been demonstrated by Liljedahl and collaborators [126] who found no changes in citrate synthase when incorporating 20min rest between sprints.

The use of near infrared spectroscopy (NIRS) allows for researcher to view through the skin at the changes in concentration of oxy and deoxyhemoglobin as well as total blood flow. Using the NIRS to collect data we can view possible improvements in microcirculation function. While SIT is limited in the ability to provide a strong stimulus for microcirculation improvements [130], COPD subjects would likely have a lower minimum stimulus required for adaptations to occur just as the general population has a lower minimum stimulus needed for adaptations compared to athletes.

The Aim of this study is to test the effectiveness of SIT in COPD patients to improve exercise tolerance. I hypothesized that SIT can be effective at improving exercise tolerance and that microcirculation improvements will play a role.

Methods

Design

This single center, controlled intervention study, was conducted at St. Olav's University Hospital in Trondheim, Norway from November 2018 to March 2019. Subjects of both groups went through a pretest week, 3 weeks of training, and a posttest week. The study was approved by the regional committee for research ethics (2018/723/REK nord) and is registered in the clinical trials database (NCT03735615).

Subjects

The subjects were allocated to two groups: COPD patients and healthy, age matched controls. The COPD patients were recruited from St. Olav's Hospital, Trondheim in association with lung specialist affiliated with the study. COPD patient inclusion criteria included: diagnosis of COPD and the ability to come in for exercise testing/training 3 times a week for 3 weeks. COPD subject's exclusion criteria included the presence of: cardiovascular disease, cancer, or other major medical conditions, injury, or illness. Subjects were also excluded if they were already receiving regular structured exercise training for their condition. Healthy subjects were recruited through contact with NTNU website and social media advertisement. Healthy subjects were interviewed by phone to further screened for specific inclusion and exclusion criteria. Inclusion criteria included: age range of 60-80 years and being available for exercise testing/training 3 days a week for 3 weeks. Exclusion criteria included: having any serious medical conditions, injury, illnesses or currently participating in regular aerobic or strength training

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±10.7	172.3±8.9
BMI (kg/m^2)	22.7±4.3*	27.1±4.5

Table 1: Baseline data are presented as mean ± standard deviation. M: male; F: female; BMI: body mass index. * p=0.044 between groups

exercise. All participants were asked not to engage in any additional regular exercise training of any kind during their time participating in the study. After screening, a total of 10 COPD patients and 9 healthy subjects were included in the study. All subjects reviewed and signed a written informed consent that was previously approved by the regional ethical committee before starting the study. COPD patients were asked to continue the use of any medications they may use regularly.

Test Procedures and Materials

Our initial assessments took place over 3 sessions within a week at St. Olav's University Hospital. This pretesting week immediately preceded the start of training. Within the 3 meetings; biopsies were taken, treadmill work economy (TWE), cycle work economy (CWE), cycle VO$_2$peak (VO$_2$peak), and cycle time to exhaustion (TTE) tests were administered. Post testing was done exactly as pretesting 48 hours after of the last training session. The only difference was a lack of the familiarization to the testing equipment. A simplification of the experimental procedure is displayed in figure 1.
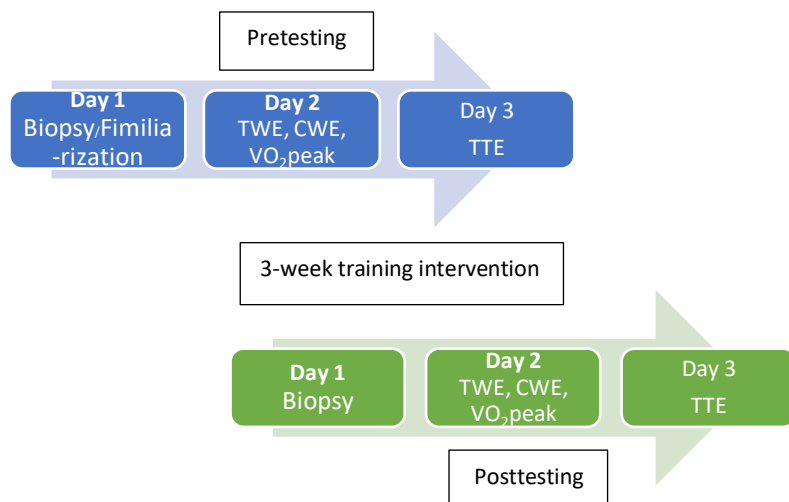

Figure 1: Simplified Experimental procedure. (TWE=Treadmill Work Economy) (CWE=Cycle Work Economy) (TTE=Time to Exhaustion)

Day 1 was designated for biopsy and familiarization with the equipment that testing would be done with. After biopsy, subjects came into the lab to walk on a treadmill (WoodWayPPS 55 Med, Woodway, Weil am Rheim, Germany), cycle on the cycle ergometer (Lode Excalibur Sport 9259000, Lode BV, Groningen, The Netherlands), get fitted for a CPET mask, and learn more about what the testing and training will consist of. During treadmill walking familiarization we found the desired intensity for future TWE test. Familiarization to treadmill walking varied in time between subjects depending on their previous history of treadmill use. For those who have used a treadmill frequently in the past familiarization was as short as 5mins, for those who have never used a treadmill familiarization lasted as long as 25mins. We continued familiarization until subjects felt comfortable without holding onto the side rails and stride looked natural. For our COPD subjects, TWE intensity was set as a

"comfortable walking pace"; a speed the subjects would walk if they were walking on the sidewalk. For our healthy subject, we aimed to find the pace and inclination to elicit a rating of 13 on the Borg scale. The reason for this discrepancy lies in the reason for the testing itself. The purpose of this test was to see if the cycle SIT training would have a crossover effect on walking economy which has a more "real world" application to improving lives of the COPD patients. For our healthy patients, we speculated that walking at a comfortable pace with no inclination may not be a high enough intensity, relative to VO_2max, to see any difference in O_2 consumption even if cycle training can improve walking WE.

In a similar fashion, we used familiarization to the cycle ergometer to find necessary parameters for the future tests. We found and saved the specific seat and handlebar position for each subject in their own profile within the Lode software so that conditions were as close to identical as possible from pretesting, through training, to post-testing. After fitting the cycle position, subjects began cycling and adjusted the load to elicit 13 on the Borg scale of perceived exertion (REF) which was recorded and later used during the cycle WE test. This was done with all subjects in the same manner.

Day 2 was designated as the "Mask" day with all the CPET testing done in one session; this includes TWE, CWE, and VO_2peak. Prior to exercise testing, resting cardiovascular measurement were done. These measurements included resting heart rate (RHR), stroke volume (SV), cardiac output (CO), and blood pressure (BP) after 10 minutes of lying in a supinated position in a dark, quite room. The resting measurements were completed using PhysioFlow (PhysioFlow, PF-05 Lab1, Manatec Biomedical, France) and CasMed 740 (CAS Medical Systems, Inc, CT, USA). CPET was done using Metalyzer II-R2 (Cortex Biophysik GmbH, Leipzig, Germany). Turbine volume calibration prior to COPD testing was done specifically for "seriously limited patients" as suggested by the manufacturer.

Both TWE and CWE tests lasted 5 minutes with the average values of each variable during the last 30s used as the outcome. TWE HR was recorded with a Polar H10 HR sensor (Polar Electro Oy, Kempele, Finland). For CWE and VO_2peak, cardiovascular measurements were recorded using the previously mentioned PhysioFlow. To remove the confounding factor of cadence on O_2 consumption and other variables, we asked the subjects to cycle at a cadence ±3 RPM from their pretest cadence. The CWE test served as the warm up for the cycle VO_2peak test which immediately proceeded it. The VO_2peak test was administered with a step protocol with

subjective estimation of appropriate increments based on WE load as suggested by the ATS.[137] For COPD patient, the step increments were 5-10W per minute. For healthy subjects, the step increments were 15-25W per minute. Protocols, specific to each subject, did not change pre-post testing. In this study, WRpeak during VO_2peak is defined as the highest work load maintained for 10s.

VO_2peak tests continued until volitional exhaustion or a clear plateau of VO_2 was observed with continual increased in workload. All subjects received verbal encouragement when RER approached 1.00 or signs of exhaustion were observable. All COPD subjects had their SpO_2 monitored using a reflectance pulse oximeter sensor during the VO_2peak testing for safety concerns. (Nonin Xpod Model 8000R, Nonin Medical Inc., MN, USA). A drop in SpO_2 below 80% when accompanied by symptoms and signs of severe hypoxemia was criteria for ending the test as suggested by the ATS.[137] Subjects that had a drop in SpO_2 below 90% during the test were candidates for additional monitoring during training for safety concerns. Some healthy and many COPD subjects very much disliked the mask. Doing the TWE, CWE, and cycle VO_2peak all in one day reduced the perception of how much the mask was actually used.

Day 3 was reserved for the TTE test. Subjects had a 5-minute warm up cycling at the same load as the WE from the previous testing day. Immediately after the 5 minutes ended the work load changed to 80% WRpeak obtained in VO_2peak test.[46, 95, 137, 138] Subjects cycled to volitional exhaustion. The end test criteria was when cadence dropped below 40 RPM, which the subjects were unaware of. Subjects were verbally encouraged as fatigue became evident. If subjects reached the 20-minute mark they were asked to rate their exertion on the Borg scale. A rating of ≤17 warranted an increase of intensity by 5w for COPD subjects and 10w for healthy subjects, to keep the increases relatively similar. This was repeated every 5 minutes from the 20-minute mark to avoid overly lengthy tests. If the rating was ≥18 then the test continued without increase as exhaustion is expected soon.

Near Infra-red Spectroscopy

The portable NIRS apparatus (PortaMon, Artinis Medical Systems, Elst, The Netherlands) utilizes a 2-wavelength continuous system simultaneously using the modified Beer-Lambert and spatially resolved spectroscopy methods. Using the differences in absorption characteristics of light at 760 and 850 nm, changes in total hemoglobin (tHb), oxyhemoglobin (HbO_2), and deoxyhemoglobin (HHb) is measured and recorded at 10Hz. More in-depth

discussion on the methodology has been repeated in pervious literature.[139-141] These variables are reported as changes ($\Delta\mu M$) from baseline, a 30s averaging before testing. Tissue saturation index (TSI) is expressed in % and is calculated as ($[HbO_2]/([HbO_2]+[HHb])\times100$). TSI reflects the dynamic balance between O_2 supply and O_2 consumption.[141]

The PortaMon device was placed on the protruding muscle belly of the vastus lateralis (VL) on the right leg. Subjects sat in a chair with the right knee at a 90° angle of flexion and were asked to engage the quadricep if the muscle belly was not obvious. Measurements were taken from the patella to ensure identical placement throughout all tests. A second, "backup" NIRS device was secured to the muscle belly of the gastrocnemius on the right leg. Similar to the VL protocol, the knee was at 90° of flexion and the subjects were asked to engage the gastrocnemius if the muscle belly was not obvious. Measurements were then taken from the tibial tuberosity to ensure identical placement throughout all tests. Gastrocnemius NIRS measurements were not analyzed as this muscle group has little relevance to cycling as compared to VL measurements. Upon removal of the PortaMon devices, a noticeable imprint of the photodiode and the light emitting diodes were noted after every test day on every subject validating the lack of movement over the skin and ensuring that the target muscle locations were the only locations measured. The PortaMon devices were affixed to the skin with medical tape (3M™ Medical Tape Medipore™ ClothTape) then securely wrapped with a sports bandage to ensure they stayed in place and to keep out any ambient light.

NIRS Variables

Reoxygenation rate ($\Delta O_2 Hb$ in $\mu M \cdot s^{-1}$) is used in this study to detect changes in microcirculation function. A linear regression analysis of the first 15s proceeding the termination of pedaling after the TTE was used.[142, 143] The reoxygenation rate is dependent on the supply of O_2 from microcirculation and the rate of O_2 consumption by the muscle over the analysis period.[140, 142-144] Therefore, to segregate and discuss microcirculation the analysis period must be short so that O_2 consumption at the muscular level changes minimally while microcirculation function after the release of muscle contraction changes. Previous literature analyzing this variable show no real consensus on appropriate time. Analysis periods and protocols vary vastly. 15s was chosen to reduce the effects of movement artifacts on the measurement while maintaining minimal changes in O_2 consumption.[143, 144] The TTE test was chosen as the test to measure this variable. From pilot testing, it seemed that in healthy

individuals, the TTE test resulted in more prominent muscular O_2 desaturation when compared to the VO$_2$peak. It appeared that it was more likely that subjects would end the VO$_2$peak test due to cardiopulmonary symptoms of exhaustion and "feeling out of breath." Almost all subjects ended the TTE test due to peripheral muscular fatigue. To obtain the smoothest recovery slopes a strict and immediate protocol was required. The protocol after completion of TTE was to immediately support the pedals with a wooden block to ensure total muscle relaxation and continue NIRS recording until the hyperemic response plateaued.

Maximum muscle desaturation during exercise (ΔTSI_{min}) was analyzed in TTE. Lower values in ΔTSI_{min} signify greater O_2 demand relative to supply.[139, 145] ΔTSI_{min} was calculated with 30s average of pretest relaxation and an average of the last 30s of exercise. Maximum increase in tHb post exercise (ΔtHb_{max}) was analyzed 60s after the termination of the TTE. During analysis tHb at the start of recovery is set to 0 so the 60s measurement is reported in $\Delta\mu M$. Detecting changes in this variable pre-post would reflect changes in blood volume/flow during recovery.[139, 145]

Training interventions

The chosen intervention was SIT. SIT on the cycle ergometer was carried out 3 times a week for 3 weeks, 9 total sessions. The sessions were meant to be identical between groups except for the amount of rest between sprints. Every session for every subject started with a 5-minute warm up at the same work load as the VO$_2$peak test and TTE warm ups. After warming up, the sessions consisted of 4 (:20s) Wingate sprints. The sprints were separated by 3min recovery for healthy, and 3-5min recovery for COPD patients depending on their individual needs, disease severity, and level of dyspnea. Cool down was determined by the subject themselves and was not specifically built into protocol. Total time per session (not including cool down) was exactly 15m and 20s for healthy subjects and on average 18m and 32s for the COPD group. There is a total of 1:20min of supramaximal intensity cycling for every subject during every session.

During recovery the subjects were informed that they did not need to cycle but could totally rest if desired. For the few, more severe, COPD patients taking advantage of total rest; a reminder to start cycling again was given a minute prior to the next sprint. To keep peak power of the sprints comparable pre to post testing we instructed subjects to maintain 70rpm in the 30s preceding the sprint. If this was not done subjects would quickly learn it was advantageous to

start the sprint at a higher cadence to achieve a higher peak. The first session was an introduction to the training and a way for us to perfect the intensity of the sprints. The Wingate torque factor was adjusted higher or lower depending on peak RPM and power of the first sprint. After tweaking, we found the torque factor for each subject that would elicit the highest peak power possible with a clear fatigue as the sprint went on.

None of the healthy subjects showed improvements in sprint capacity or recovery that demand a change in training stimulus variables. Due to the nature of the disease, the COPD patients sometimes had "good days" and "bad days" in which recovery periods could be shortened or elongated if needed. As a research group, we took the consideration of unequal recovery between group as a possible limitation but decided getting the optimal training stimulus possible for the COPD patients was worth the limitation of varying recovery times. As mentioned previously, COPD patients that had and SpO_2 drop below 90% had additional SpO_2 monitoring during training to ensure safe practice.

Statistical analysis

Analysis of most of the collected data was processed through SPSS using paired sample t-test when data was normally distributed and Wilcoxon rank test when not. Pearson correlations analysis were used to analyze the relations between variables and test outcomes. NIRS data was processed with MATLAB to confirm signal quality, normalize the data, compute group means, delta changes, and calculate reoxygenation rate.

Results

Participants

Figure 2 displays the flow of participants from initial contact to final analysis. Of the 19 subjects tested at baseline, 17 subjects completed posttesting. Two subjects in the COPD group dropped out during the intervention due to illness, leaving n=9 in the COPD group and n=8 in the Healthy group. One subject in the COPD group was omitted in TTE analysis due to protocol implementation errors. Therefore, a total of 16 subjects were analyzed for the main outcome, n=8 in the COPD group

Subject Flow Diagram

Assessed for eligibility

Excluded (n=2)
♦ Not meeting inclusion criteria (n=2)

COPD Group   Healthy Control

Allocation

Allocated to intervention (n=10)
♦ Received allocated intervention (n=10)

Allocated to intervention (n=9)
♦ Received allocated intervention (n=8)
♦ Did not receive allocated intervention

Follow-Up

Discontinued intervention (Illness) (n=1)
Lost to follow-up (Illness) (n=1)

Discontinued intervention (n=0)
Lost to follow-up (n=0)

Analysis

Analysed (n=8)
♦ Excluded from TTE analysis (protocol failure) (n=1)

Analysed (n=8)
♦ Excluded from NIRS data analysis (subcutaneous fat layer obstructed NIRS) (n=2)

Figure 2: Subject Flow Diagram. (TTE=Time to Exhaustion) (NIRS=Near Infrared Spectroscopy)

and n=8 in the Healthy group. Baseline characteristics of the participants are displayed in Table 1. The COPD group showed a significantly lower BMI (p=0.044) compared to the Healthy Control.

TTE and Wingate

Both COPD and Healthy groups showed significant improvements in TTE of 49% (p=0.046) and 70% (p=0.009) respectively. (Figure 3) Both COPD and Healthy groups also significantly improved peak power output (PPO) in the :20s Wingate test, by 13.8% (p=0.007) and 19.2% (p=0.011) respectively. (Figure 4)
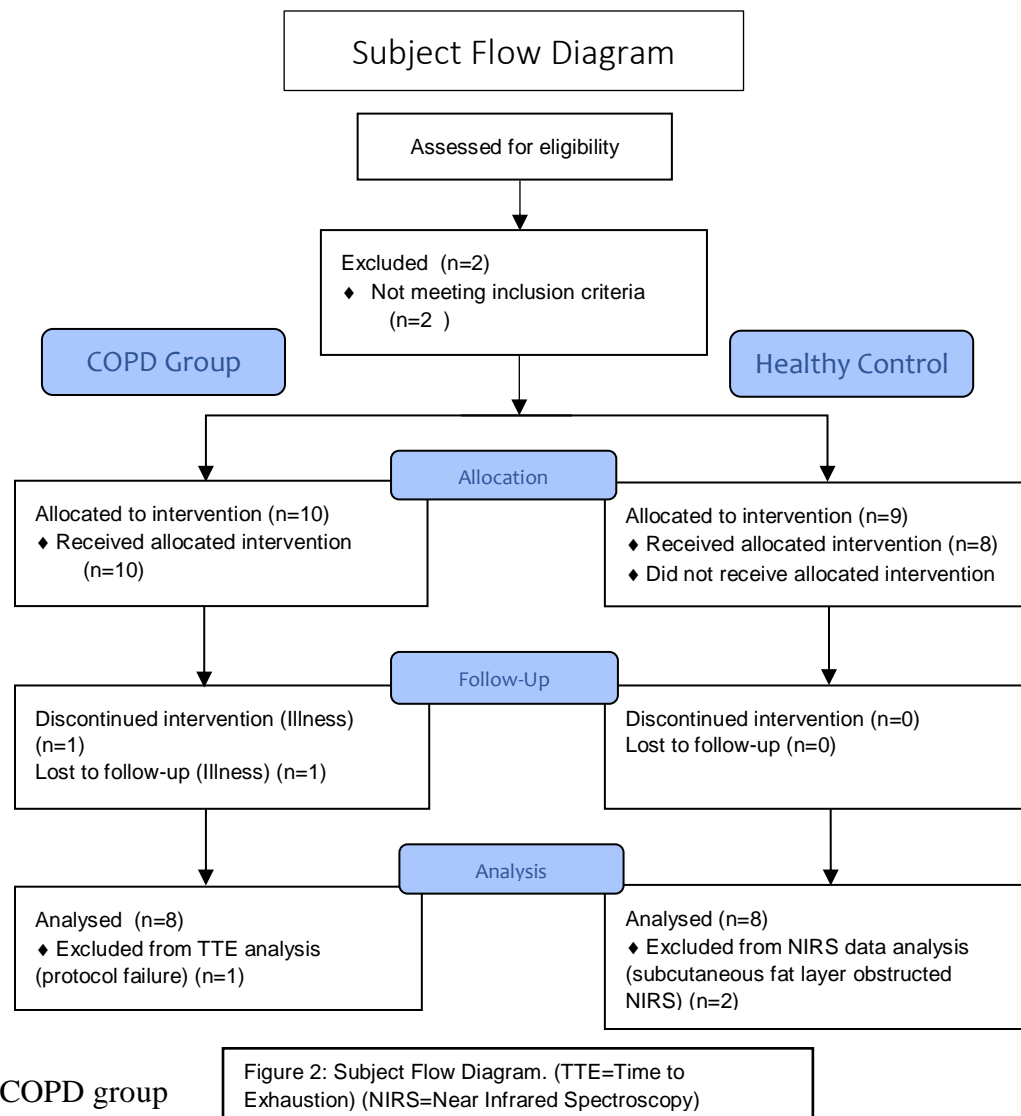
| | | COPD Group | | | | | Healthy Group | | | |
	N	Pre Mean	Post Mean	ΔMean	P-value	N	Pre Mean	Post Mean	ΔMean	P-value
TWE (mL/kg/min)	8	12.7 ±2.2	12.9 ±2.3	0.2 ±1.5	0.71	8	17.0 ±2.5	17.0 ±2.8	0.0 ±1.0	0.92
CWE (mL/kg/min)	8	11.5 ±3.5	12.0 ±3.3	0.5 ±1.1	0.24	8	19.2 ±4.6	19.5 ±4.4	0.3 ±1.5	0.58
VO_2peak (L/min)	8	1.21 ±0.45	1.27 ±0.53	0.06 ±0.15	0.30	8	2.53 ±0.91	2.67 ±0.83	0.14 ±0.17	**0.09†
VO_2peak (mL/kg/min)	8	17.5 ±4.3	18.4 ±5.5	0.9 ±2.4	0.30	8	30.8 ±7.8	32.6 ±7.1	1.8 ±2.5	**0.09
VO_2peak (mL/kg^67/min)	8	70.1 ±18.4	73.8 ±23.1	3.7 ±9.3	0.30	8	131.6 ±36.1	139.1 ±32.4	7.4 ±10.1	**0.076
WRpeak (W)	8	81.9 ±32.4	87.5 ±40.0	5.6 ±11.1	0.20	8	211.9 ±68.9	224.4 ±62.3	12.5 ±15.6	**0.058
HbO_2 RR (µM/s)	8	0.056 ±0.021	0.060 ±0.008	0.004±0.014	0.44	6	0.065 ±0.001	0.062 ±0.006	-0.003 ±0.006	0.28
ΔTSI_{min} (ΔµM)	8	-3.70 ±2.74	-2.81 ±3.70	-0.89 ±5.33	0.65	6	-2.72 ±4.04	-2.09 ±3.01	-0.63 ±2.29	0.53
ΔtHb_{max} (ΔµM)	7	9.43 ±4.97	14.95 ±5.29	5.52 ±3.09	*0.003	6	9.23 ±5.91	6.13 ±4.40	-3.10 ± 6.49	0.30
Skinfold VL (mm)	8	10.6 ±1.9	-	-	-	6	14.1 ±2.9	-	-	-

Table 2: Pre and post data are presented as mean ± standard deviation. Mean change is mean within group change ± standard deviation. P-values of the change are shown in separate columns. Related-Samples Wilcoxon Signed Rank Test (†); Statistically Significant Change (*); Approaching Statistical Significance (**). (TWE = treadmill work economy) (CWE = cycle work economy) (HbO_2 RR = HbO_2 Recovery Rate) (ΔTSI_{min} = Difference between TSI baseline and minimum TSI measured during testing) (ΔtHb_{max} = difference between tHb at the end of exercise testing and tHb 60s into recovery) (Skinfold VL = Skinfold Vastus Lateralis)
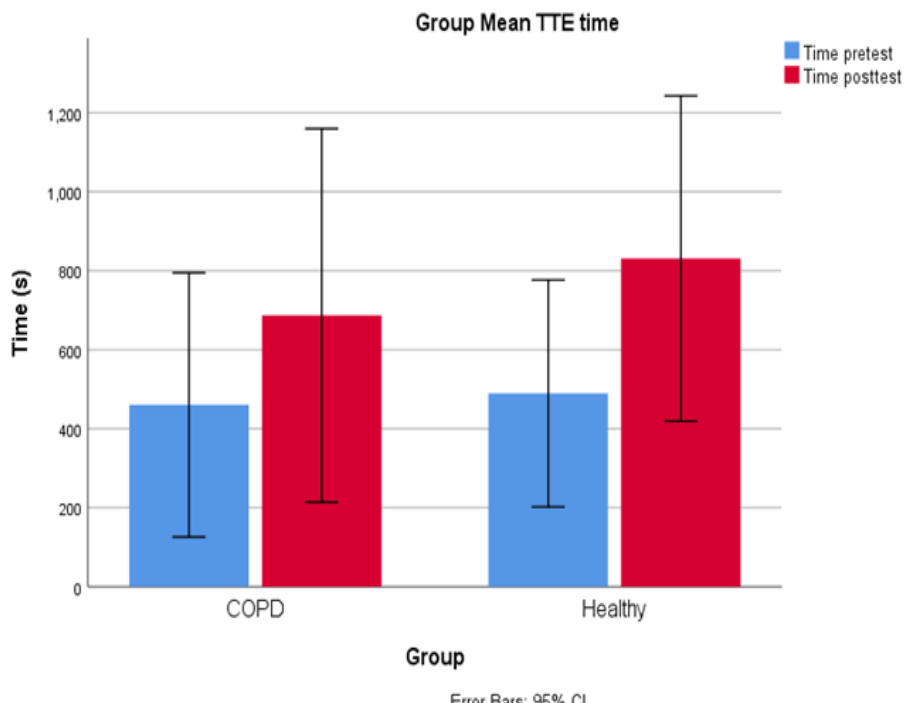

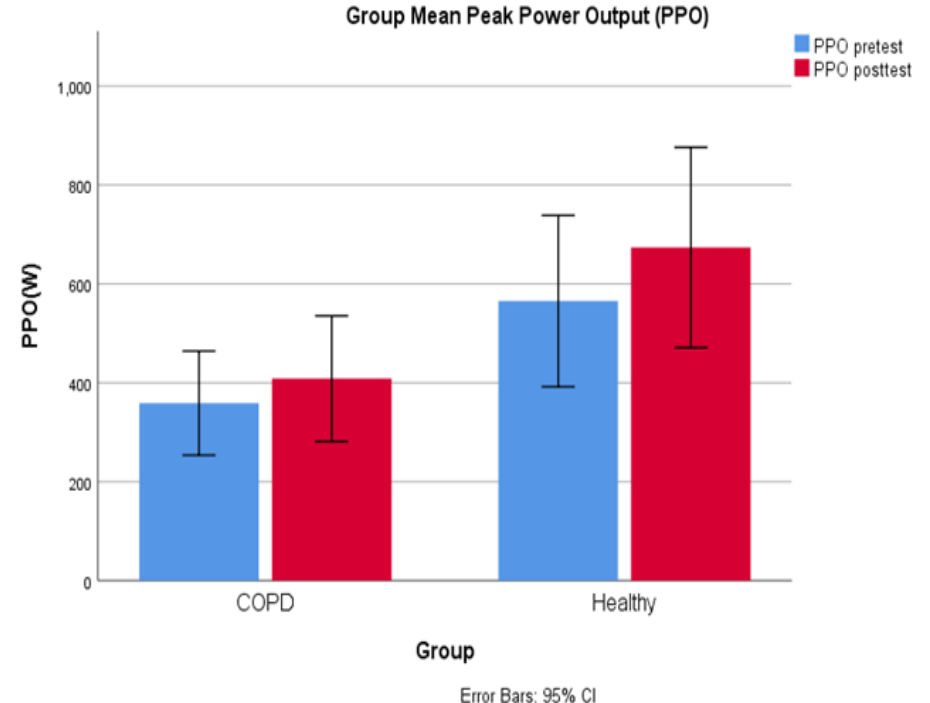Figure 3: Group Mean Time to Exhaustion changes. (s=seconds)

Figure 4: Group Mean Peak Power Output changes. (W=watts)

VO$_2$peak and Work Economy Tests

VO$_2$peak showed no significant changes in the COPD group. In the healthy group, there was a trend towards VO$_2$peak improvement (p=0.089). This was the same case when analyzing absolute VO$_2$peak and while allometrically scaled. WRpeak improved in the healthy group (p=0.001) but not in the COPD group. (table 2) No other variables obtained during CPET showed any significant changes. No analyzed variables in both TWE and CWE showed any significant changes.

NIRS

ΔtHb_{max} showed a significant increase in the COPD group (p=0.003) by 60% while no change was found in the Healthy group.(Figure 5 & 6) Reoxygenation rate and ΔTSI_{min} show no change pre to post test in either group.
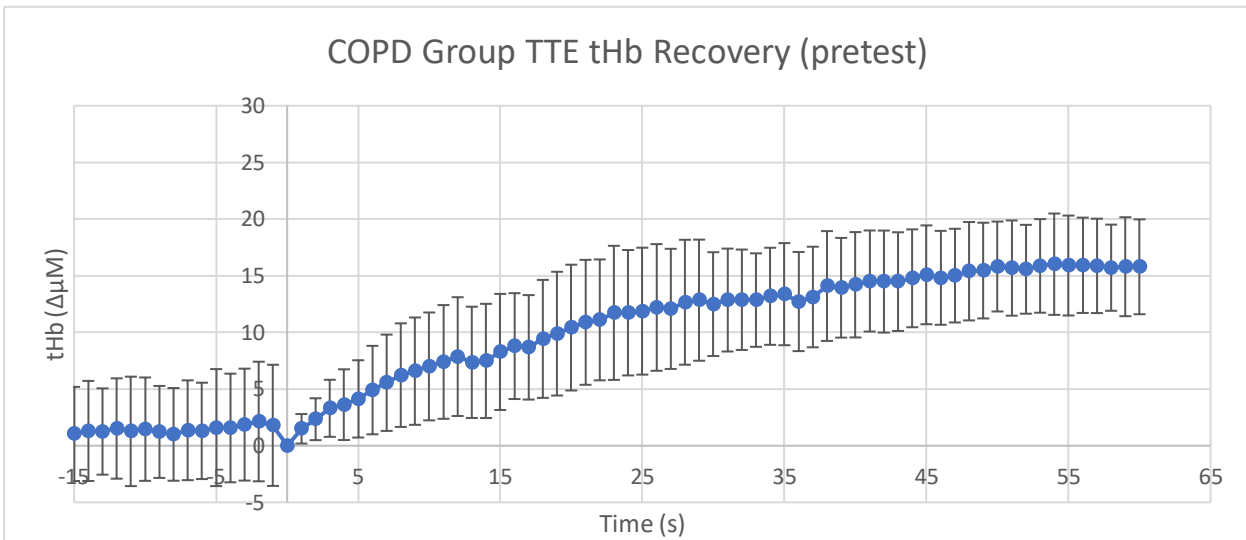
Figure 5: COPD group TTE tHb recovery pretest. (tHb=total hemoglobin) (TTE=Time to Exhaustion)
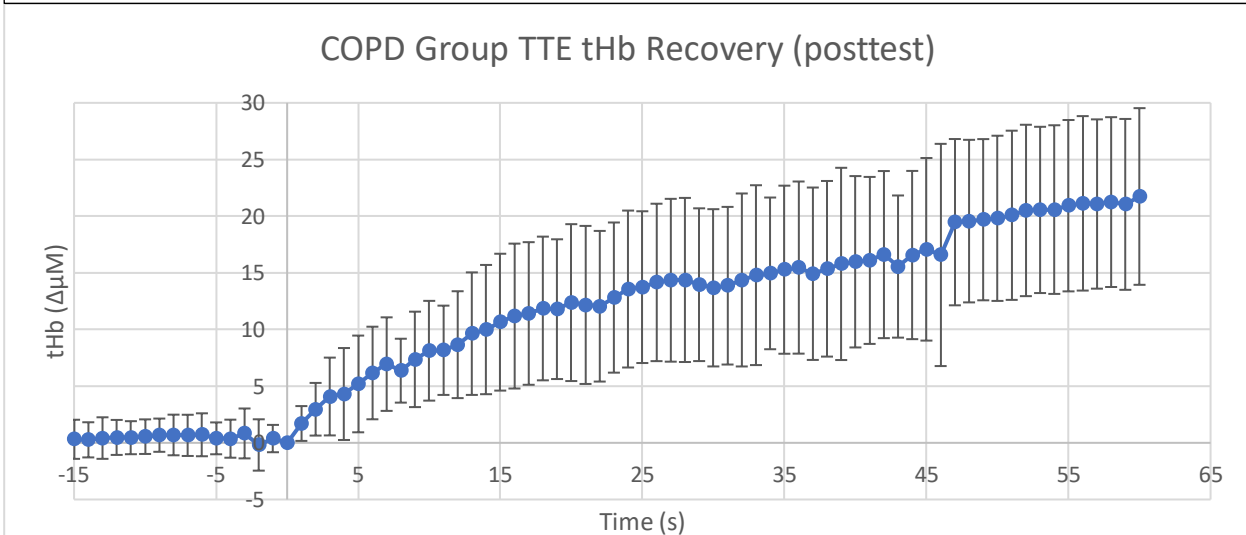
Figure 6: COPD group TTE tHb recovery posttest. (tHb=total hemoglobin) (TTE=Time to Exhaustion)

Discussion

The major novel finding of this research is that 4x:20s sprints, 3xweek for 3 weeks (36 sprints, 12min) significantly improved COPD patients average TTE by 3:47min (p=0.046), a 49% improvement on baseline measurements. For comparison, a randomized trial of respiratory rehabilitation (24weeks), inpatient for 8 weeks and supervised outpatient for 16 weeks created an average improvement of 4:42min (p=0.0005).[88] This was a comprehensive respiratory rehabilitation including: stretching, breathing techniques, strength training, upper and lower body endurance training, and whole body interval training with progressions. While the previously mentioned study did not use cycling as training, we found no improvements in cycling work economy that could confound the comparison. The previous study also used a TTE intensity of 60% WRpeak rather than 80% used in the present study. TTE improvements are commonly used as a marker of the success of rehabilitation for COPD.[46, 85, 95] "Cycle endurance time is a valuable outcome as it is related to multiple clinical aspects of disease severity in COPD. Improvement in TTE after pulmonary rehabilitation can reflect a total improvement of clinical status in patients with COPD."[138] The ATS/ERS statement discusses an expected TTE increase of 80% citing several pulmonary rehabilitation studies; all lasting 8-12 weeks.[95] To our knowledge this is the first study to show that SIT can be an effective training protocol to improve endurance performance in COPD patients.

The age matched control group significantly improved their TTE on average 5:42min (p=0.009), a 70% improvement from baseline measurements. Bailey and collaborators saw a 53% improvement in TTE after 6 SIT session in young healthy subjects.[131] The current study has 33% more training session and 27% more improvement than Bailey et al. suggesting that the effect in youth was mirrored in older adults and the effect did not plateau. Burgomaster and collaborators reported 100% increase in TTE after just 6 SIT sessions in young healthy subjects.[128] In Burgomaster's study, the subjects had 30s sprints and up to 7 sprints per session which was not feasible in our experimental groups, this could explain the discrepancies. SIT's potential for performance improvements are highlighted in this study; even in otherwise sedentary older adults. To our knowledge this is the first study to display the effectiveness of SIT to improve endurance performance in sedentary older adults.

Wingate

In the current study Wingate sprints were not just the method of training but a test in itself. In this fashion, we could monitor how improvements in training performance provoked the improvements seen in other tests. Both COPD group and healthy control group significantly increased their peak power output (PPO) in a 20s Wingate test by 49.51W (p=0.007) and 108.42W (p=0.011) respectively. Both COPD and healthy groups showed a large improvement in PPO from baseline (13.8% and 19.2% respectively), far beyond what Gibala and collaborators found in young healthy subjects (5.4%).[129] The current study training intervention lasted 33% longer but Gibala et al. had more sprints per session. This vast difference in results could be due to the COPD and older sedentary adults having a lower baseline power and therefore more potential for improvement. It is also likely that the subjects in our study were not accustom to such strenuous and demanding testing as young healthy men during baseline measurements despite similar amounts of familiarization.

The large PPO improvements recorded in this study is a great accomplishment which could have the potential to improve the subjects' daily lives. Older adults who had higher peak anaerobic power output measured from Wingate test also had higher physical function capacity as reported from the Continuous Scale Physical Functional Performance Test (CS-PFP).[146] The CS-PFP is composed of 16 everyday tasks including making a bed, stair climbing, transferring laundry, and getting down and up from the floor according to standardized instruction.[147] The ability to complete these daily tasks is typically diminished in COPD patients. More daily physical activity as measured by accelerometry is associated with a slower decline of lung function.[75] Large PPO improvements in both of these subject groups from time efficient SIT provide sound reasoning for future research to explore the causality behind this anaerobic training improving abilities to complete ADLs.

Training Induced Improvements in TTE

Increases in PPO relate to increases in force production by the working muscles [148] and/or improved mechanics. The later was minimized by familiarization to sprints prior to the first training day, using the second training day as the pretest measurement, and a strict protocol of 70±5 RPM at the start of the sprint. Because strength measurements were not done, we can only suggest the lower body force production has improved rather than just body mechanics and technique improvements. Muscular weakness in COPD patients is known to limit their

performance in endurance tests, and those with stronger peripheral muscle typically perform better.[51] This may explain the near correlation with PPO improvements and TTE improvements in the COPD group (r=0.727, p=0.64, figure 14).

PPO improvements was not found to correlate with the improvements in TTE in the healthy group (p=0.493). This is likely because the healthy population was stronger and may not be limited by muscular weakness to the degree that the COPD patients were. Cantrell and collaborators found no improvements in TTE after only strength training in healthy individuals while those who did strength training and SIT did have an improvement.[149] It seems that the required increase in muscular strength to improve TTE in healthy subjects may be beyond the capabilities of this short term SIT protocol. This argument is strengthened by Simpson et al. showing that with 8 weeks of strength training improving COPD patients TTE by 42% [89] which was not found by Cantrell et al. with healthy subjects.

The relationship between strength and aerobic performance has been analyzed exceedingly in previous literature. It seems that improvements in rate of force development (RFD), more so than improvements in one repetition max (1RM), are the predominant cause of improvements.[9, 150] Improvements from strength training improve work economy which then improve aerobic performance. Hoff and collaborators speculate that increasing maximal strength makes a standard submaximal load relatively easier requiring less MU recruitment. It could be possible that blood flow restriction from muscular contractions are reduced as well due to decreases in active muscle for the workload.[9]

While these concepts could have certainly been in effect to improve the TTE result, CWE did not show any changes in either group. If cycling economy improved during the TTE but not CWE the explanation could lie in the intensity of the test. The training in this study was always at a supramaximal level. The training shows a strong possibility for muscular strength improvement which should lead to CWE improvements. According to the Henneman's size principle, the smallest and weakest MU are recruited preferentially, then the larger stronger MU as necessary. It could be that the CWE intensity was too low, possibly recruiting about the same number of smaller weaker MU posttest as pretest showing no economy improvements. The TTE at 80%WRmax may have been at an intensity high enough to have significant changes in economy due to some of the larger inefficient MU being recruited pretest, and not recruited posttest.

It has also been established that SIT recruits higher proportion of type IIx fibers compared to MICT [131] and stimulates adaptations to shift them to type IIa.[126, 129, 132, 133] This concept backs up the theory that the supramaximal training used in this study could show improvements in aerobic performance in higher relative intensities while showing no improvements in CWE at lower relative intensities. Because VO2peak showed no significant changes as well, the cause of TTE cannot be that the test was simply at a lower relative VO_2 posttest. Clearly, the factors responsible for training induced improvements in exercise capacity are exceptionally complex, intertwined, and determined by many physiological systems. I assessed three local muscular blood flow factors that could shed light on peripheral adaptations to SIT that can affect aerobic performance.

NIRS

Reoxygenation rate (ΔO_2Hb in $\mu M \cdot s^{-1}$), thought to be closely related to microcirculation capabilities, did not significantly improve in either group. (Figures 8-11) This is not such a surprise as SIT's ability to improve microcirculation indices is naturally limited due to lower volume of training.[130] Angiogenesis is principally dependent on providing shear stress to the luminal side of blood vessels which is accomplished by MICT but very limited in SIT.[151] It is important to note that this measurement of the speed of HbO_2 influx post exercise is not a biopsy. While it seems that microcirculation function did not improve, it does not mean that number of capillaries around a fiber (Ncaf), capillary to fiber ratio(C/F_i) capillaries/mm^2 of muscle, and CFPE index did not change. While the results of this study as well as previous literature would point to little changes in microcirculation from SIT; future studies should use biopsies to fully answer the question of microcirculations role in improved submaximal performance in COPD.

On the contrary, the COPD group's ΔtHb_{max} improved by 60% (p=0.003). This refers to 60% greater increase of total hemoglobin 60s after the TTE test at posttest compared to pretest. (Figure 5 & 6) Whether the increased hyperemic response is due to increased microcirculation or increased vasodilation is unknown.[152] Though the rate at which recovery start immediately post exercise (reoxygenation rate) did not change in this study, 60% more blood flow to recovering muscle 60s post exercise would suggest an overall faster recovery to homeostasis.

There are several possible reasons why blood flow (ΔtHb_{max}) increased without a concomitant increase in reoxygenation rate (ΔO_2Hb) in the COPD group. It could be that O_2 delivery by the microcirculation did increase along with a similar increase in O_2 consumption by

improved mitochondrial function which is to be expected with SIT. If both factors improved to a comparable degree that could explain no significant changes in reoxygenation rate pre to post testing but an increase in $\Delta tHb_{max.}$. Another factor that could influence reoxygenation rate is the SpO_2. The average SpO_2 for the COPD group during the VO_2peak test was 88%. While ΔtHb_{max} is unaffected by the oxygen saturation of blood, reoxygenation rate certainly can be.

A more likely reason for the discrepancy is methodological faults. Reoxygenation rate is often done in more perfect environments. Reoxygenation rate is observed in smaller muscle mass that is exercising under arterial occlusion, leading to essentially complete muscle desaturation.[143, 153, 154] When the arterial occlusion is removed, the slope is steeper with less movement artifacts as well. It is not easy to get subjects to be perfectly still after exercise to volitional exhaustion in major muscle groups rather than in smaller muscle groups like the forearm. On the contrary, Buchheit and collaborators have found improvements in reoxygenation rate after a longer training intervention and after sprints.[142] Many of the COPD subjects had tremors; after exercise this was more prominent, which also created movement artifacts which effects the calculated slopes. Again to the contrary, Luis Puente-Maestu et al. found improvements in COPD patients reoxygenation rate, though with a different methodology, 3x the training duration per session and double the sessions which are important factors for angiogenesis.[155] ΔtHb_{max} however, requires less perfection as 60s is already passed the exponential increase in blood flow so the ability to detect changes is simpler and easier in practice. Again, future studies looking at the changes in microcirculation in COPD post training should use the more direct measurement of muscle biopsies to quantify microcirculation if its available.

The healthy group saw no changes in ΔtHb_{max}. Neither group saw any changes in ΔTSI_{min} in the TTE, suggesting that subjects did not change how much muscle O_2 desaturation occurred during the TTE test even though test lasted longer. This was not a surprise, it seems that both groups in both pre and posttest reached a similar level muscular O_2 desaturation before termination of test. No NIRS measurements correlated with changes in TTE, the main outcome of the study. With no VO_2peak improvements, no detected microcirculation function improvements, and no detected CWE improvements, it would seem likely that the vast improvements found in both groups' TTE results come from mitochondrial adaptations and improvements in strength for the COPD group. This is backed by the ample literature on SIT's
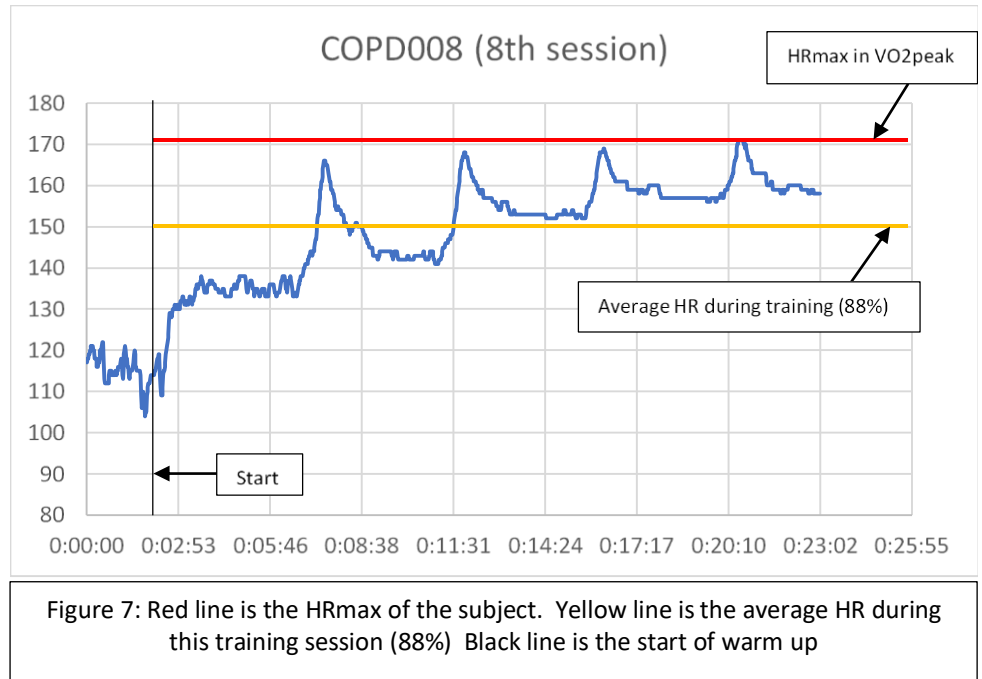
effects on mitochondria.[30, 122-126, 128, 129, 131-133, 156] Which factor contributed more for the COPD group cannot be concluded as I do not have access to my colleague's mitochondrial data.

VO$_2$peak

The limited effectiveness of SIT on improving VO$_2$peak was apparent in this study. When observing the effect of SIT in the healthy group with an average VO$_2$peak of ($30.8mL\cdot kg^{-1}\cdot min^{-1}$ ±7.81), there was an average increase of ($1.78mL\cdot kg^{-1}\cdot min^{-1}$) but this did not reach statistical significance (p=0.089). Two subjects had pretest values above the average for their age group when compared to HUNT 3 data which is based on treadmill not cycle.[157] These two subjects would be expected to have even higher VO$_2$peak on a treadmill and did not exactly fit the descriptions of sedentary older adult. When observing the effectiveness of SIT in the healthy group without these above average subjects, the effects were more substantial. This group (n=5) had an average relative VO$_2$peak of ($26mL\cdot kg^{-1}\cdot min^{-1}$ ±4.87) and significantly increased (p=0.018) by an average of ($3.23mL\cdot kg^{-1}\cdot min^{-1}$) or 12.4%. SIT can be effective at increasing VO$_2$peak, but only in subjects with lower baseline aerobic capacity.[123, 127, 128] This adjustment in analysis was strictly to express the idea in the previous sentence and the omission of these two subject's data was not applied to any analysis.

Despite the COPD group having below average CRF, we saw no statistically significant improvements in VO$_2$peak, assessed in relative or absolute terms. Minor improvements that can be seen in healthy subjects can be clouded by the disease which is the limit to VO$_2$peak both pre and posttest. It seemed that as the onset of dynamic hyperinflation progressed, subjects quit for fear of the consequences of overexertion, a relationship that has been previously exposed.[158] To quote a subject "I could have continued but I would have to go to a bad place"; to avoid serious dynamic hyperinflation that would require substaintial time to alleviate. Because the subjects had "good and bad days" and always had their own psychological limitations surrounding dynamic hyperinflation, true peak values in CPET were not reached.

The use of supplemental O_2 may have been a useful alternative as the disease becomes less of a limiting factor allowing for a more accurate CPET. Using a VO_2peak predictor based on a submaximal performance, not restricted by the fear of serious dynamic hyperinflation, may have been a better strategy as well.[59] The example of

Figure 7: Red line is the HRmax of the subject. Yellow line is the average HR during this training session (88%) Black line is the start of warm up

HR during training in a COPD patient (Figure 7) reinforces the previous concept. During training several COPD subjects were able to reach HRs higher that their HRmax reached in the VO_2peak test which suggest that the VO_2peak test was hindered. In this specific subject, their training elicited an average HR of 88% of HRmax and reached just above their VO_2peak HRmax.

Limitations

The original plan for the study was to compare two groups of COPD patient but recruitment was more challenging than expected. For this reason, we could not compare the effect of SIT on COPD to another training protocol. We also had less subjects than planned which lowered the power for statistical analysis. With the heterogeneity of COPD as a disease and within our group, having as many subjects as possible is important. FEV1 and FEV1:FVC data on the COPD and healthy subjects exists but due to logistical problems this data was not obtained before the submission deadline. Because of this I could not confirm that the healthy group was, in fact, without COPD even in the mildest form. I also could not categorize the severity of COPD within the COPD group. Subjects who volunteered for this study were motivated to improve themselves; the clinical application would likely lack such motivation. There was no controlling of nutrition or acute tobacco use which could affect performance in all tests. Due to the COPD subjects having "good and bad days" sometimes subjects had more and less rest period then healthy subjects. Therefore, COPD subjects did not have identical training

stimulus when compared to the healthy subjects and when compared to each other within the group. The difference in starting VO2peak, body mass, and training stimulus limited our analysis on comparison of the groups because it would be difficult to determine whether the differences are due to the disease or other factors. The testers could not be blinded to which group subjects were in due to safety concerns.

To discuss microcirculation, reoxygenation rate analysis period must be as short as possible to avoid mitochondrial respiration from decreasing which would affect the measurement. I chose 15s which has been seen in previous literature on non-occlusion reoxygenation.[142, 143] This was to avoid the confounding effect of movement artifacts on the calculation of the slope. It would be more accurate to measure reoxygenation rate in a three second span if movement artifacts could be totally avoided. Some researchers have found that exercise intensity can affect reoxygenation rate [155, 159, 160] while others have not found this relation.[161] Because WRpeak significantly improved in the healthy group as well as some of the COPD subjects, the posttest TTE would be at a lower relative intensity. This would be a confounding factor. It may have been better to measure this variable after the last Wingate sprint in the first and last train session. Lastly, I could only speculate on mitochondrial improvements as the measurement has not been analyzed yet.

Conclusion

In conclusion, SIT proves to be effective at improving TTE in both COPD and sedentary older adults. This submaximal exercise improvement is independent of any microcirculation indices measured in this study. In those with mild to moderate COPD, SIT could be a great "kickstart" to rehabilitation allowing subsequent training to be at higher relative intensities for more effective training and faster rehabilitation. This may not be true for more severe patients as they tend require much more external motivation and tend to fear dynamic hyperinflation more than more subjects with more mild cases of COPD.

Acknowledgments

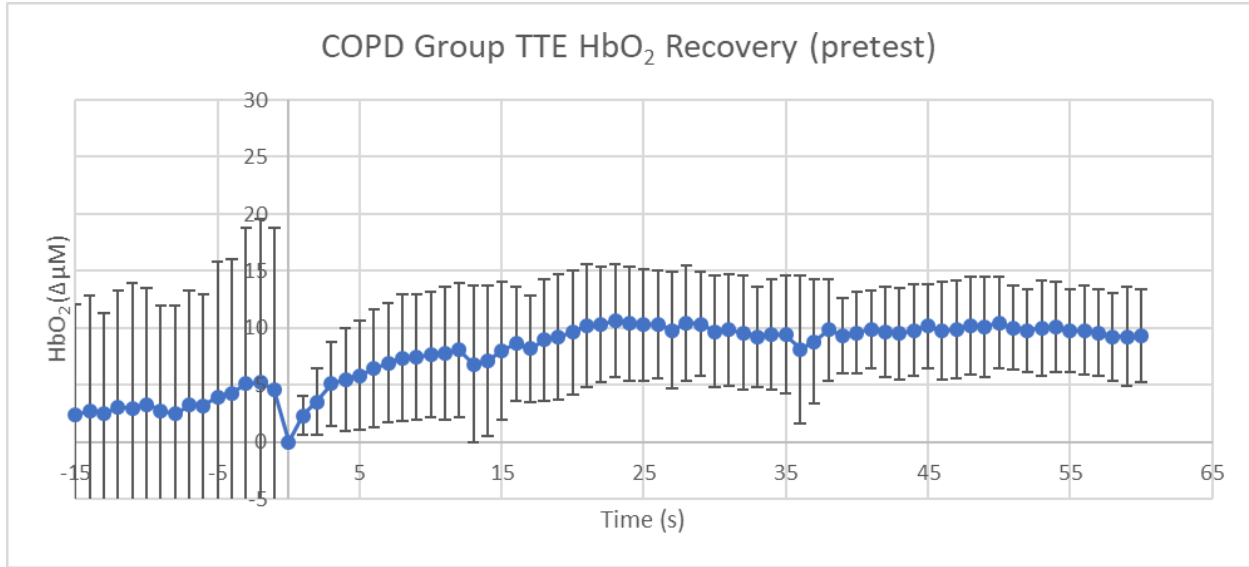# Appendix

NIRS Graphs

(group mean with std bars)

Figure 8: COPD group TTE HbO$_2$ Recovery pretest. Only the first 15s is used for analysis. (TTE=Time to Exhaustion)(HbO$_2$=oxyhemoglobin)
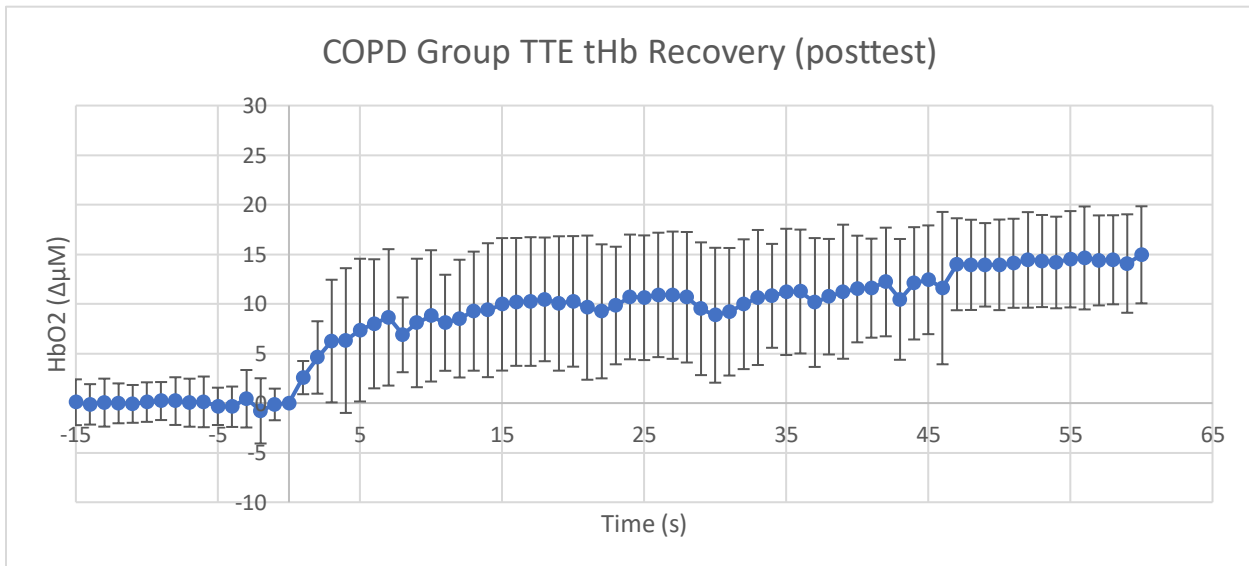

Figure 9: COPD group TTE HbO$_2$ Recovery posttest. Only the first 15s is used for analysis. (TTE=Time to Exhaustion)(HbO$_2$=oxyhemoglobin)
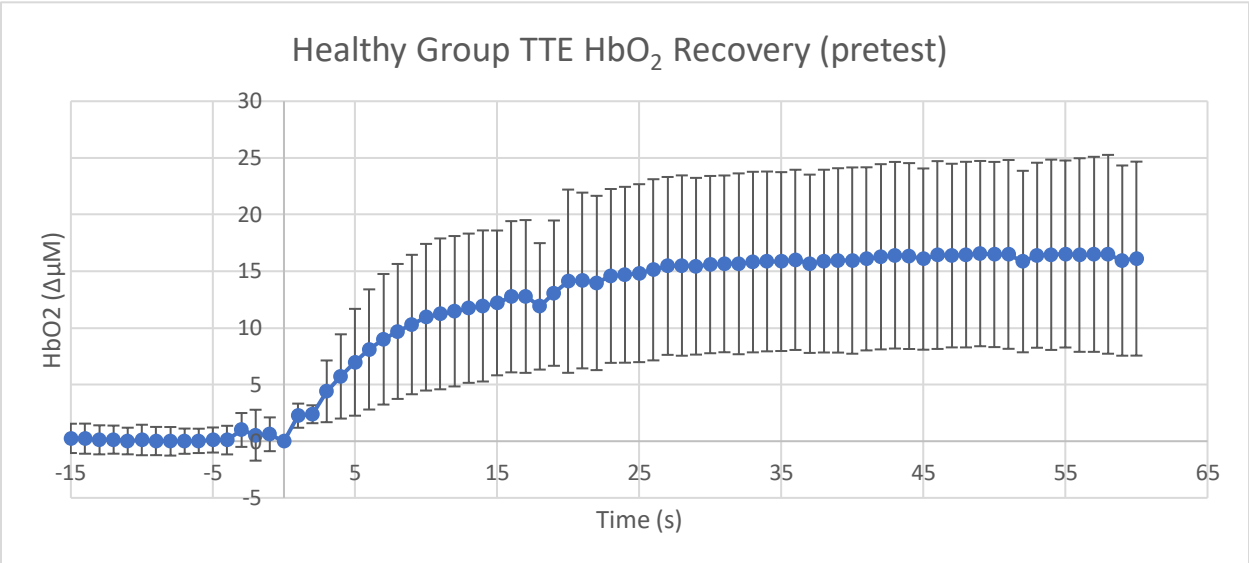
Figure 10: Healthy group TTE HbO$_2$ Recovery pretest. Only the first 15s is used for analysis. (TTE=Time to Exhaustion)(HbO$_2$=oxyhemoglobin)
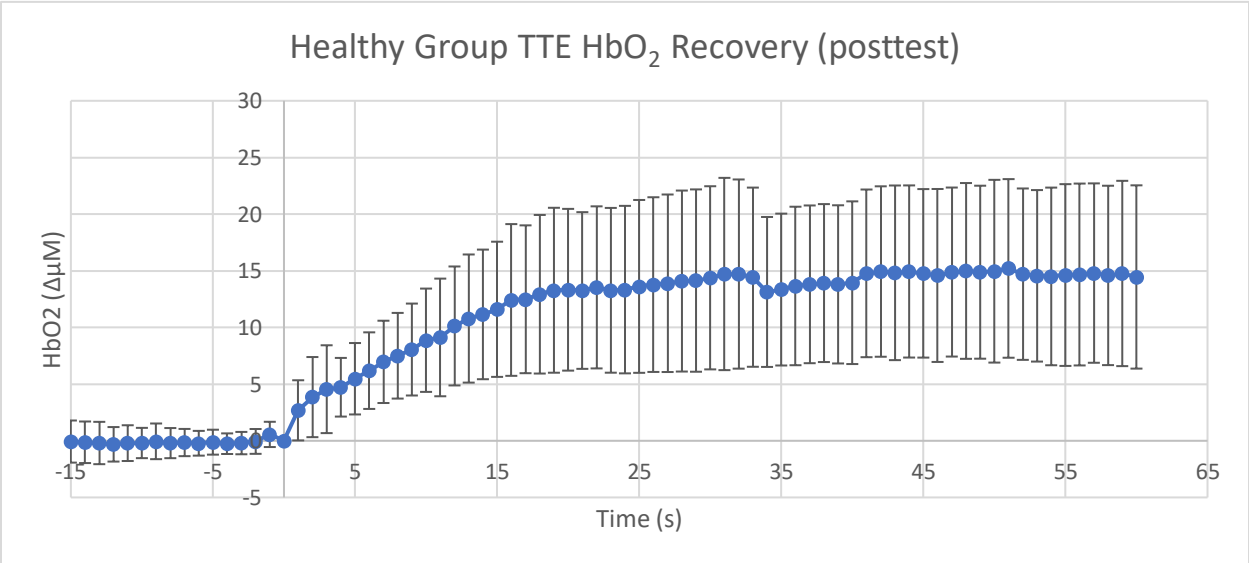

Figure 11: Healthy group TTE HbO$_2$ Recovery posttest. Only the first 15s is used for analysis. (TTE=Time to Exhaustion)(HbO$_2$=oxyhemoglobin)
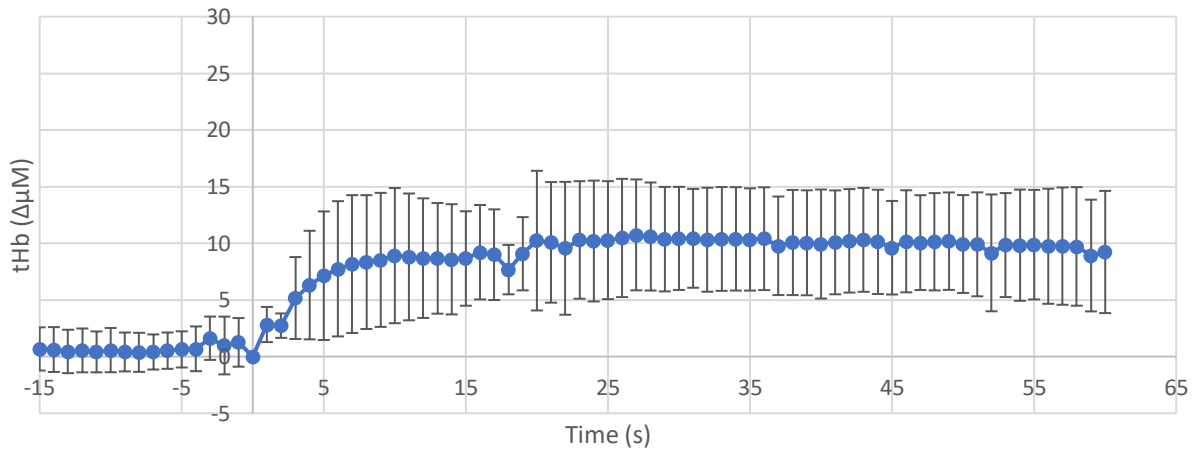
Figure 12: Healthy group TTE tHb Recovery pretest. The calculation of ΔtHbmax was the difference between the 60s measurement and the normalized (zeroed) end test measurement. (TTE=Time to Exhaustion)(tHb=total hemoglobin)
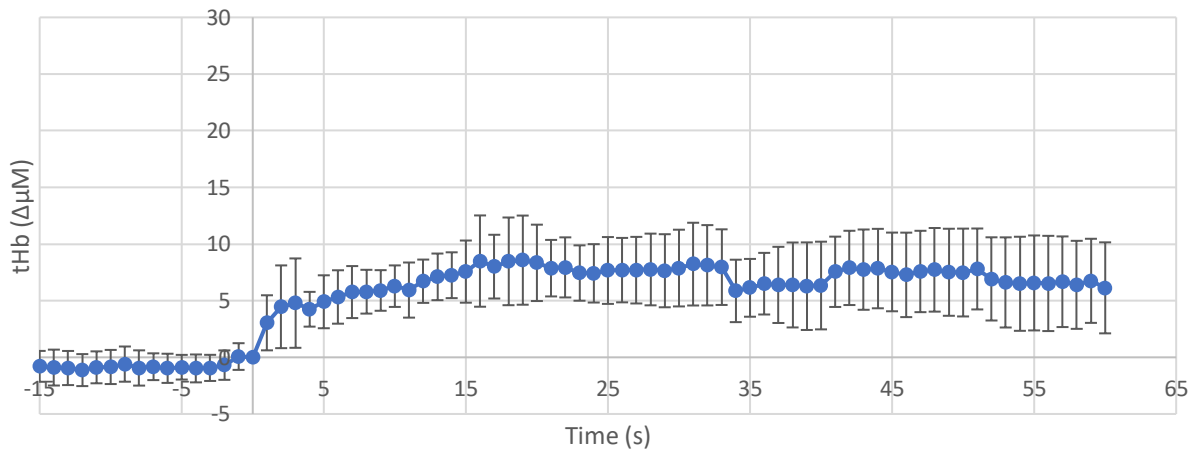

Figure 13: Healthy group TTE tHb Recovery posttest. The calculation of ΔtHbmax was the difference between the 60s measurement and the normalized (zeroed) end test measurement. (TTE=Time to Exhaustion)(tHb=total hemoglobin)
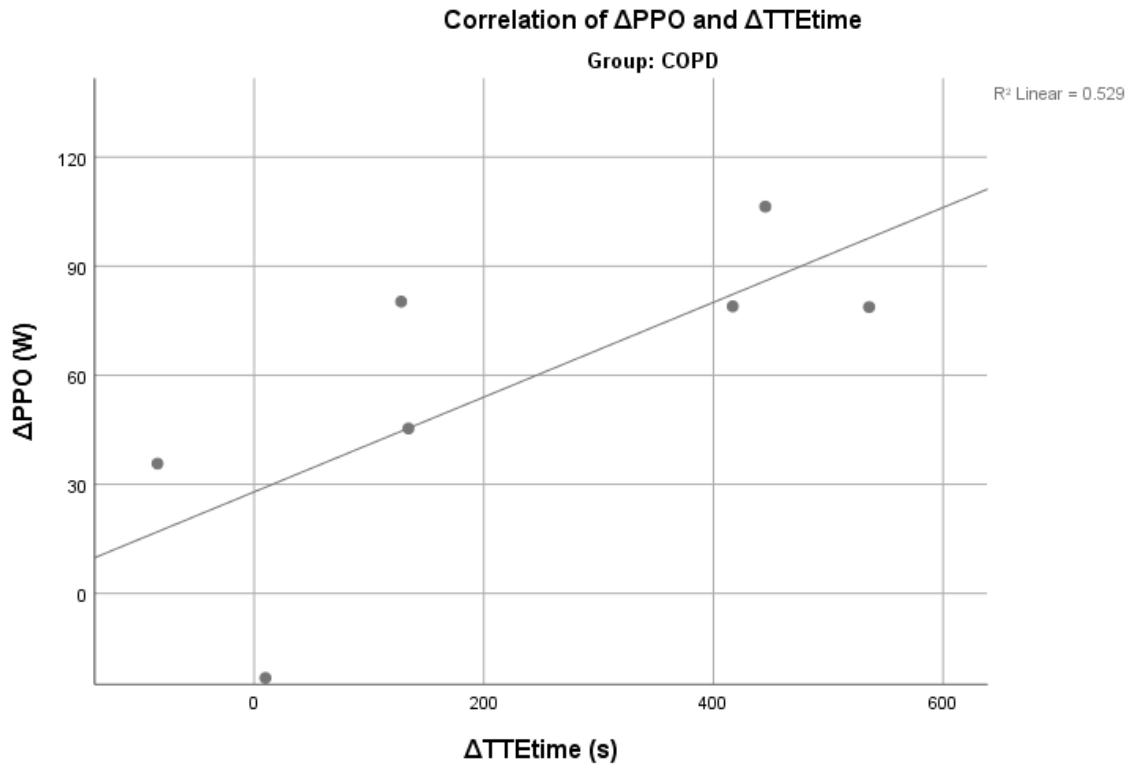
Figure 14: Correlation of change in PPO and change in TTE time in the COPD group. (p=0.064) (r=0.727) (PPO=Peak Power Output) (TTE=Time to Exhaustion)

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