Siri Bjørgen

Aerobic high intensity interval training is an effective treatment for patients with Chronic Obstructive Pulmonary Disease

Thesis for the degree of Philosophiae Doctor

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Norwegian University of Science and Technology
Faculty of Medicine
Department of Circulation and Medical Imaging

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Aerob høy intensitets intervall trening er en effektiv behandling for pasienter med kronisk obstruktiv lungesykdom

Aerob høy intensitets intervallsykling ved 85-95% av peak hjertefrekvens forbedrer peak oksygen opptak og maksimal yteevne hos pasienter med kronisk obstruktiv lunge sykdom. Ett bens sykling gir større økning i helkropps peak oksygenopptak sammenlignet med to bens sykling. Hos ett bens gruppen gjør en og en fot hver for seg en større jobb enn når begge føttene jobber samtidig, uten at ventilasjonen er forskjellig. Derfor gjør ett bens sykling det mulig for pasientene å jobbe med en høyere muskel spesifik intensitet sammelignet med to bens sykling som resulterer i en betydelig bedre treningsrespons.

Aerob høy intensitets ett bens sykling ved 85-95% av peak hjertefrekvens i normoksi og hyperoksi forbedrer peak oksygenopptak og maksimal yteevne hos pasienter med kronisk obstruktiv lungesykdom. Å puste inn 100% oksygen under trening øker ikke peak oksygenopptak ytterligere sammenlignet med å puste romluft. Heller ikke ved akutt måling av oksygenopptaket er det forskjell mellom å puste i hyperoksi og normoksi, selv om den arterielle oksygen metningen i blodet er betydelig høyere i hyperoksi før og etter treningsperioden, noe som indikerer en oksygen forbruks begrensning i de perifere musklene.

Aerob høy intensitets intervalltrening i hyperoksi ved 85-95% av peak hjertefrekvens øker peak oksygenopptak, maksimal yteevne, arbeidsøkonomi og livskvaliteten hos pasienter med kronisk obstruktiv lungesykdom som har oksygen metningsfall (SpO_2<88%) ved maksimal aktivitet. En oksygen forsynings begrensning er synlig hos pasientene med kronisk obstruktiv lungesykdom gjennom et betydelig høyere peak oksygenopptak og en bedre yteevne når de puster ekstra oksygen sammenlignet med romluft under testing før og etter treningsperioden. På den andre siden ser vi ingen akutt forskjell i peak oksygenopptak mellom hyperoksi og normoksi hos pasientene med koronar hjerte sykdom, noe som indikerer en oksygen forbruksbegrensning hos disse pasientene.

Bakgrunnen for å gjennomføre studiene var å finne trenings metoder som gjorde at pasienter med kronisk obstruktiv lunge sykdom som i utgangspunktet er ventilatorisk begrensede, kunne holde en aerob høy intensitet over en periode der både hjertet og de perifere musklene fikk optimal stimulering. I tillegg ønsket vi å undersøke i hvilken grad pasientene er begrenset av oksygen tilførselen til muslkaturen eller av oksygen forbruket i muskelen når det gjelder peak oksygenopptak. Studiene er gjennomført som kontrollerte treningsintervensjoner med testing av utholdenhet før og etter 8 uker med høy intensitet intervall trening.

Siri Bjørgen
Institutt for Sirkulasjon og Bildediagnostikk
Veiledere: Jan Helgerud (hovedveileder), Jan Hoff og Sigurd Steinshamn

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Preface

The following thesis is based upon a summary, an introduction to the field and the papers listed below, referred to by roman numerals in the text. The work of this thesis was carried out in the laboratory of Exercise Physiology and Sports Sciences at the Department of Circulation and Medical Imaging, The Faculty of Medicine, The Norwegian University of Science and Technology and is to be concluded with the degree PhD in clinical medical research.

Paper I:

Siri Bjørgen, Jan Hoff, Vigdis S. Husby, Morten A. Høydal, Arnt E. Tjønna, Sigurd Steinshamn, Russell S. Richardson, Jan Helgerud. Aerobic high intensity one and two legs interval cycling in Chronic Obstructive Pulmonary Disease; the sum of the parts is greater than the whole. *Eur J Appl Physiol. 2009 (Epub ahead of print).*

Paper II:

Siri Bjørgen, Jan Helgerud, Vigdis S. Husby, Sigurd Steinshamn, Russell S. Richardson, Jan Hoff. Aerobic high intensity one leg interval cycling improves peak oxygen uptake in Chronic Obstructive Pulmonary Disease patients; no additional effect from hyperoxia. *(Under review in Int J Sports Med).*

Paper III:

Helgerud J, Bjørgen S, Karlsen T, Husby VS, Steinshamn S, Richardson RS, Hoff J. Hyperoxic interval training in chronic obstructive pulmonary disease patients with oxygen desaturation at peak exercise. *Accepted in Scand J Med Sci Sports. 2009.*

Summary

Aerobic high intensity interval cycling at 85-95% of peak heart rate improves peak oxygen uptake (VO_{2peak}) and performance in severe chronic obstructive pulmonary disease patients (COPD). One leg cycling demonstrates greater improvement in whole body VO_{2peak} than two legs cycling. The work load performed leg by leg in the one leg group is greater than when both legs are working together, however the ventilatory load is not different. Thereby the one leg cycling allows the patients to train at a higher muscle-specific intensity compared to whole body exercise, resulting in a significantly greater training response.

Aerobic high intensity one leg interval cycling at 85-95% of peak heart rate in normoxia and hyperoxia improves VO_{2peak} and performance in patients with severe COPD. However, breathing 100% oxygen during training does not improve VO_{2peak} above the level attained by breathing ambient air. Neither does acute hyperoxia increase VO_{2peak} compared to normoxia despite a higher arterial oxygen saturation during testing both before and after the training period, which indicates an oxygen demand limitation to VO_{2peak} in the peripheral muscles in both stages.

Hyperoxic aerobic high intensity interval training at 85-95% of peak heart rate increases VO_{2peak}, performance, work economy and quality of life in severe COPD patients with hypoxemia (SpO_2< 88%) at peak exercise. Oxygen supply limitation is demonstrated in the COPD group by a significant improved VO_{2peak} and performance in acute hyperoxia compared to normoxia during testing both before and after the training period. On the contrary, no acute difference between hyperoxia and normoxia suggests an oxygen demand limitation in the coronary artery disease patients (CAD).

1 Introduction

Chronic obstructive pulmonary disease (COPD) is one of the most common causes of death in most countries, and the only common cause of death in the Unites States that has increased over the last 40 years, in sharp contrast to the reduction in cardiovascular and infectious diseases [1]. COPD was the sixth leading cause of death in 1990 and is estimated to become the third leading cause of death worldwide by 2020, mostly related to the expanded epidemic of smoking and the increasingly older population [2, 3]. The disease causes increase of chronic disability and is predicted to become the fifth most common cause of chronic disability worldwide by 2020 [3, 4]. COPD is also one of the most common reasons for sick leave from work, placing an enormous and increasing economic burden on the society [3, 5]. The World Health Organisation (WHO) have estimated that currently 80 million people have moderate to severe COPD and that more than 3 million people died from the disease in 2005, approximately 5 % of all deaths globally [2]. The prevalence of COPD is related to age and smoking but is found to be underestimated due to unawareness of the disease in subjects suffering from COPD. In addition, a lack of correct diagnostics in those seeking medical advice is frequent [6]. It is demonstrated that hospitalized patients with COPD has a higher hospitalization prevalence and in-hospital mortality from co-morbidities such as hypertension, diabetes, coronary artery disease, heart failure, pulmonary infections, cancer, and pulmonary vascular disease than the COPD itself [7, 8]. Chronic lung disease has a significant impact on cardiovascular function due to an increased right ventricular afterload caused by increased pulmonary vascular resistance resulting from structural changes in the pulmonary circulation, as well as hypoxic pulmonary vasoconstriction [9].

Patients suffering from COPD are physiologically limited by the inability to engage in the usual activities of daily living due to reduced pulmonary function and poor exercise capacity [10, 11]. Exercise intolerance progresses relentlessly as the disease advances and can lead to virtual immobility, social isolation and eventually early death [12].. Evidence based guidelines for pulmonary rehabilitation by the American association of cardiovascular and pulmonary rehabilitation in conjunction with the American College of Chest physicians, list exercise training as a mandatory component of pulmonary rehabilitation for patients with COPD [13].

A strong correlation between endurance capacity expressed as maximal oxygen uptake (VO_{2max}) and the risk for mortality has been demonstrated in both healthy subjects and those

with cardiovascular disease [14], while improvements in aerobic capacity reduces the mortality risk [15]. Exercise capacity is found to be a predictor of mortality in COPD independent of the FEV_1 and that VO_{2peak} is an excellent predictor of long-term survival [16]. VO_{2max} is defined as the highest rate at which oxygen can be taken up and utilized by the body during exercise with large muscle groups [17, 18]. An increase in VO_{2max} by only 3.5 ml oxygen pr. kg bodyweight resulted in 12 % improved survival [14]. Since most COPD patients show extremely poor exercise performance [19, 20], and the exercise capacity declines over time [21], these findings highlights the importance of exercise among COPD patients to increase their quality of life and to prevent an early death [22]. The pulmonary damages related to COPD are not reversible even by cessation of smoking [23], and thereby the single most important factor to treat the disease and increase life expectancy is to increase the patient's aerobic endurance capacity [13].

1.1 Aerobic endurance

Aerobic endurance depends on the ability to perform large-muscle, whole body exercise at moderate to high intensities for expended periods of time and is determined primarily by VO_{2max} and to a lesser degree of the lactate threshold and work economy [17]. The importance of a superior aerobic endurance capacity is best exposed in elite athletes competing in different sports with continued exercise [24], whereas the significance of being physical fit in non athletes and patients is often neglected. The importance of an increased aerobic endurance capacity is highlighted by the fact that it might prevent an early death in those with genuine low exercise capacity and increase quality of life in healthy people [14]. VO_{2max} is considered to be the present "gold standard" for measurement of cardiovascular fitness and is a useful parameter for determining aerobic endurance also for patients with COPD [25].

1.2 Maximal oxygen uptake

VO_{2max} is the single most important physiological measurement of aerobic endurance [26] and relates to the highest rate at which oxygen can be transported from ambient air to the working skeletal muscles and utilized during severe exercise. It depends on oxygen transport from the atmosphere to the muscle mitochondria and reflects the combined functional capacities of the cardiac output, the oxygen carrying capacity of the blood and the oxidative capacity of the active skeletal muscle [17, 18, 27]. Oxygen uptake (VO_2) is the product of cardiac output

(CO) and the arteriovenous oxygen difference ([(a – v) O_2 difference]) and is given by the Fick equation:

$$VO_2 = CO \cdot (a - v)\ O_2 \text{ difference} \quad (1.1)$$

Cardiac output is a product of the heart rate and stroke volume of the heart. The variation in oxygen delivery to locomotor muscles is solely a function of the size of the stroke volume, as maximal heart rate and arterial oxygen content both are unaffected by training [28]. Endurance trained individuals with a high VO_{2max} have both a superior capacity to deliver and utilize oxygen than untrained individuals [24]. VO_{2max} varies among individuals due to factors such as body size, muscle mass, genetics, age, gender and conditioning status [17, 29]. When comparing elite endurance athletes and ordinary subjects, total hemoglobin and arterial oxygen saturation remains equal. Muscle oxygen extraction percentage is higher, however insufficient to account alone for the elite level of performance. The most important difference is found in maximal cardiac output with values twice as high documented in the elite athlete [30, 31]. VO_{2max} is task specific and has been found to be 10-20 % lower in biking compared to walking/running [32]. VO_2 increases linearly with increasing power output and reaches a plateau with further increases in work rate at VO_{2max}. However in many subjects, as the work rate increases, termination of work is demonstrated before this plateau is reached [31]. In such situations where the VO_{2max} criteria are not fulfilled, the term peak oxygen uptake (VO_{2peak}) is more commonly used which is the highest level of oxygen that can be taken up and utilized by the body during exercise under a given condition (e.g. reduced muscle mass, in untrained individuals or disease). In patients with cardiovascular and pulmonary disease it might be angina pain or ventilation that limits the work intensity and the term VO_{2peak} is thereby used [33, 34].

1.3 Limitations to VO_{2max}

A plateau of VO_{2max} is evidence of maximal metabolic oxidative phosphorylation that can reach maximum ATP generation and not a limitation *per se* of oxygen limitation of VO_2 [31]. This means that every step of the oxygen cascade from the air into the mitochondria is a potential deterrent for VO_{2max}. If the oxidative phosphorylation is limited by the availability of mitochondrial oxygen, which is determined by how fast the oxygen can be delivered to the muscle cell, a supply limitation is present. If the oxygen availability in the mitochondria outreaches the utilization by the oxidative phosphorylation, the system is demand limited

[31]. Wagner states that in ambient air at sea level, maximal oxygen uptake in athletic individuals is primarily set by oxygen transport limitation (i.e. cardiac output), whereas in unfit subjects, it is set by metabolic limitations [31]. This is either by a conductance/diffusion limitation [35, 36] or a limitation in the mitochondria to reach a maximum respiratory rate [37-40]. These claims are supported by the literature demonstrating that unfit individuals may be exposed to reduced or increased oxygen content without any changes in VO_2 [41]. The opposite is however the case in fit subjects and athletes [42-44]. A 2-3 times muscular overcapacity of the aerobic energy production when the whole body is employed was demonstrated by Saltin et al. [45], an evidence of supply limitation of VO_{2max} in healthy subjects during whole body work. This demonstrates that VO_{2max} is not an absolute concept, it is acutely changeable by altering parts of the metabolic pathway [31]. By calculating the contribution of the individual steps of the respiratory cascade, DiPrampero [46] concluded that for healthy humans exercising in normoxia, about 75 % of VO_{2max} is set by central oxygen transport and 25 % by the periphery.

1.4 Aging, inactivity and aerobic endurance

When evaluating COPD responses, age related physiological changes have to be taken into account as most of the individuals who are afflicted by the disease are elderly people [47, 48]. COPD often results in a progressive decline in exercise capacity, reductions in muscle mass and strength because of the vicious cycle of physical inactivity and deconditioning [1, 11, 49]. These effects are thought to be superimposed on the decline in VO_{2max}, lean body mass and muscle strength expected with an inactive lifestyle followed by aging. However regular aerobic exercise seems to prevent and restore the muscle metabolic and vascular losses in aging people [50-52] and in elderly patients with COPD [53]. It has been demonstrated that elderly people respond to high intensity aerobic interval training (85-95 % of maximal heart rate) and increase their VO_{2peak} in the same manner as young people [50, 54]**.** A decline in VO_{2max} of ≈ 10% per decade after 30 years of age has been observed in studies of healthy individuals [55, 56]. It has been found that the decline in VO_{2max} is proportional to a decreased cardiac output, peak heart rate and peak stroke volume in older subjects [57]. It is debated whether this decrease in exercise capacity is due to the ageing process or the inactivity followed by aging [58]. Studies have demonstrated that it is a result of deconditioning [59] and that endurance training prevents and restores VO_{2max} [54, 60-62]. In physical active subjects VO_{2max} remains higher at all ages compared to inactive subjects [58].

As demonstrated in the classic "Dallas bed rest study", 3 weeks of complete inactivity had the same detrimental effect on VO_{2max} as 30 years of aging [63].

1.5 COPD; the disease

COPD has been defined in the GOLD (global initiative for chronic obstructive lung disease) guidelines as a disease state characterized by airflow limitation that is not fully reversible [64]. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases [65]. Although COPD is a disease primarily affecting the lungs, it also produces significant systemic consequences [8]. COPD is a joint designation of Emphysema and Chronic bronchitis. Emphysema is defined as a condition of the lungs characterized by abnormal, permanent enlargement of air spaces distal to the terminal bronchiole accompanied by destruction of their walls and without obvious fibrosis [66]. Chronic bronchitis is defined by increased airway resistance and productive cough lasting > 3 months for at least 2 consecutive years. It results from mucus hypersecretion which leads to microscopic and macroscopic changes in the airway structure such as mucus production, epithelial changes, airway inflammation, smooth muscle cell hypertrophy and submucosal bronchial gland enlargement [67]. Most COPD patients have both emphysema and chronic bronchitis [68]. Even though there are incidences of COPD from α_1-antitrypsin deficiency [69], increased risk due to dusty environments [70] and childhood respiratory illness, which may render people susceptible to tobacco-induced lung damage [71], COPD is almost always caused by excessive cigarette smoking over many years [3, 8, 72].

The number and sizes of holes in the alveolar walls are increased in COPD and alveolar attachments to small airways are disrupted. In combination with an ongoing chronic inflammation in the airways, this leads to a remodelling and narrowing of the small airways which diminish the ability of the airways to remain open during expiration and hinders ventilation by trapping air in the bronchioles and alveoli, resulting in an increased dead space. In COPD patients, the residual lung volume increases due to a slow forced emptying of the lungs accompanied by a decreased expiratory flow rate. The airflow limitation is slowly progressive and irreversible [73-75].

COPD is diagnosed by Spirometry which measures the volume of air that is forcibly exhaled from the point of maximal inspiration, forced vital capacity (FVC), and the volume of air

exhaled during the first second, forced expiratory volume in one second (FEV_1). The ratio between these two measurements (FEV_1/FVC) is calculated, and the degree of lung function abnormality decided. A post-bronchodilator $FEV_1/FVC < 0.7$ confirms the presence of an airflow limitation that is not fully reversible. The severity of the disease has been divided into four stages which is a post-bronchodilator FEV_1/FVC ratio of < 0.70, and a FEV_1 % predicted; mild (FEV_1 >80), moderate (50 < FEV_1 < 80), severe (30 < FEV_1 < 50) and very severe (FEV_1 < 30, or FEV_1 < 50 plus chronic respiratory failure). In addition, patients who smoke or have exposure to pollutants, have cough, sputum or dyspnoea are classified "at risk" with a FEV_1/FVC ratio of > 0.70 and a FEV_1 % predicted >80 [8]. The FEV_1/FVC ratio declines with age, however the fixed FEV_1/FVC ratio of < 0.70 as a threshold for defining COPD is found reliable also in older subjects (> 65 years) [76]. It has been demonstrated that in patients with COPD, FEV_1 is the single best predictor for mortality [77].

1.6 COPD and physical activity

COPD is primarily a pulmonary disease which limits the patients' ability to breathe during graded exercise. An increased dead space/tidal volume ratio induces a ventilatory inefficiency during exercise serving as one of the main causes of decreased exercise capacity in patients with COPD [78]. Ventilation fails to keep pace with oxygen consumption as minute ventilation does not rise as much as carbon dioxide production and oxygen uptake, causing the arterial partial pressure of carbon dioxide to rise and oxygen to decrease [79]. During physical activity, increased ventilatory demands and decreased maximum ventilation leads to a decreased breathing reserve which consequently results in dyspnoea [80]. Patients with COPD have a progressively reduced exercise capacity [1, 11, 81] and the fundamental symptoms that limits exercise in most patients are dyspnoea and/or fatigue which may result from ventilatory constraints, pulmonary gas exchange abnormalities, peripheral muscle dysfunction, cardiac dysfunction or any combination of the above [9, 10, 20, 40, 82-84].

There is a growing realization that COPD is a multi- organ system disease which affects the exercise capacity by the ability to transport oxygen to the working muscles and to consume oxygen in the mitochondria [85, 86]. Patients with COPD experience a substantial morbidity from secondary impairments such as peripheral muscle, cardiac, nutritional and psychosocial dysfunction. Pulmonary rehabilitation should thereby focus on prevention and restoration of these parameters to the highest possible level of independent function which is crucial for increasing the patient's daily living and their quality of life [10, 87]. Physical training

increases capillarization [88] and mitochondrial development [89], and are maintained in proportion to the aerobic endurance of the whole organism [90], thereby an exercise training program of the peripheral muscles is recommended as a mandatory component of pulmonary rehabilitation for patients with COPD [13, 65, 91, 92].

An ongoing debate among researchers is whether COPD patients have a peripheral skeletal muscle dysfunction which might contribute to the exercise intolerance, or if similar physiologic adaptations to aerobic endurance training such as structural changes in the peripheral muscles and the cardiovascular system occur as in healthy subjects. Casaburi [48] claims that in COPD, the metabolic alterations in the muscles are evidence of a skeletal muscle dysfunction due to marked differences in lactate release, venous carbon dioxide accumulation and respiration in the leg at submaximal exercise compared to healthy individuals. On the contrary, Richardson et al. [40, 93, 94] claims that COPD patients have a skeletal muscle metabolic reserve, however they state that the skeletal muscle performance is reduced due to the muscle fibre type composition and muscle disuse. Documentation of changes in the locomotor skeletal muscles that constitute myopathy has been detected in COPD patients [81, 83, 95-98]. Deconditioning might be a possible co-mechanism in the peripheral muscle abnormalities as it has been demonstrated that skeletal muscle strength is correlated with exercise tolerance and that patients with COPD commonly possess peripheral muscle weakness [20] and excessive perception of leg fatigue during exercise [19]. Muscle wasting and reduced strength is a consequence of the inactive lifestyle in COPD patients [49, 84, 99] and gain in muscle mass and strength has been associated with better exercise tolerance and survival [100, 101].

In healthy elderly subjects as well, improvement in peripheral muscle mass and strength is associated with a better exercise capacity [102]. Healthy elderly individuals gradually experience a decreased fraction fast-twitch glycolytic type II- and increased slow-twitch oxygenated type I muscle fibres [103]. This is in contrast to COPD patients who have a decreased fraction of oxidative type I fibres compared to type II fibres [81, 94, 97] and thereby low levels of mitochondria, oxidative enzymes and decreased capillary density followed by a low capacity for oxygen consumption which is a significant contributor to work capacity limitation [49, 83, 94, 97, 98, 104-107]**.** Increased muscle strength and endurance improves muscular recruitment and oxidative capacity in the exercising muscles of COPD patients [100, 106, 108, 109]. In addition to a low proportion type I muscle fibres, a reduction

of oxidative enzyme activity is present within the type II fibres [81]. The skeletal muscle abnormalities reflected by the reduced mitochondrial (aerobic) potential and compromised oxidative phosphorylation results in an exaggerated dependence on high energy phosphate transfer and anaerobic glycolysis leading to an early onset of lactate accumulation [82, 83, 110, 111]. The early lactate accumulation in COPD may stimulate increased ventilation and hasten the onset of ventilation limitation. Reduced lactate concentration for a given exercise work load that accompanies exercise training decreases carbon dioxide output and thereby reduces the ventilation requirement allowing the patients to tolerate a given exercise level for a longer period [112]. Improved aerobic endurance and decreased levels of lactate concentration and ventilation at a given exercise level after training reflects the link between skeletal muscle function and exercise capacity in COPD [113]. Because of the ventilatory, muscular or symptom limitations at peak exercise, the heart rate is not maximally challenged in patients with COPD. A reduced stroke volume at all exercise intensities is also a consistent finding in COPD, primarily caused by reductions in right ventricular output due to lung hyperinflation, increased pulmonary vascular resistance and reduced venous return as a result of increased intra-thoracic pressure which in turn reduces left ventricular filling [9, 114].

It is widely accepted that exercise should be a basic part of any pulmonary rehabilitation program as it is the most important treatment in COPD [75]. The importance of exercise training in pulmonary rehabilitation is doubtless as it improves both exercise tolerance and health related quality of life [75, 115]. Inspiratory muscle training alone or in addition to exercise training has not been prooven superior compared to exercise training alone when concerning exercise capacity, performance or health related quality of life [116, 117]. Endurance training appears to be the best form of training compared to resistance training and ventilatory muscle training [118].

1.7 Training effects

Aerobic high intensity interval training has been demonstrated to increase VO_{2max} by 7 % in healthy active young male students [119] whereas the same training intervention has resulted in an 15 % increase in healthy elderly subjects over 65 years [54]. Aerobic high intensity interval training in patients with intermittent claudication, coronary artery disease and heart failure have demonstrated increases in VO_{2peak} by as much as 16-46 % [120-122]. The increase in $VO_{2peak/max}$ in these studies was dependent on training modality, with significant greater increase after aerobic high intensity interval training compared to their respective

control groups performing moderate intensity continuous training. In the field of COPD, the majority of training interventions use performance measured by watt, walking distance, time to exhaustion etc. as the main outcome to describe training effects. These methods are rather diffuse. Diffuse are also recommendations concerning aerobic exercise prescription in COPD patients which aims at exercise for 20-60 minutes 3-5 days a week at an intensity corresponding to 55-95% of maximal heart rate [123]. This is a very general exercise advice with no clear recommendation.

In COPD studies measuring increase in VO_{2peak}, a vide range of training interventions is used. A resemblance in these studies is adjustment of training intensity to be able to sustain the requiered duration, aiming at the highest possible intensity tolerated related to dyspnoea or based on the Borg scale [87, 113, 124-130]. The most frequent increase in VO_{2peak} is about 4-8 % after 20-30 minutes contnous work regulated by a work lolad as high as possible. However, most patients were unable to achieve the work load defined in their respecctive studies (> 70% peak work load) [87, 113, 124, 125, 127]. Some studies actually demonstrate no increase in VO_{2peak} after 10-12 weeks of training. These training interventions consisting of 40-45 min continous moderate-low intensity training (50-60% peak work load), high intensity short interval (30 sek) training (100% of peak work load) [131, 132], and high intensity (90% of peak work load) short intervals (1 min) [133]. One study lasted 10 weeks, with 5 trainings pr week for 80 minutes, consisting of 2 min low intensity (>50% peak work load) interval cycling for 20 minutes, and 60 minutes of other exercise activities, without any increase in VO_{2peak} [129]. Some studies demonstrate greater increases in VO_{2peak} >10%. Studies consisting of >30 moderate-high intensity (60-70% of peak work load) continous training sessions has found increase in VO_{2peak} by 10-17% [126, 133, 134], whereas greater increase (~20%) has been demonstrated after 15 min one leg high intensity training (50% of two legs peak work load) [128].

1.8 Training intensity

Several studies have demonstrated that training intensity is the most important factor concerning improvements in aerobic endurance and VO_{2max} in both healthy subjects and patients [119-122, 135-138]. Intensities up to 90% of VO_{2max} in healthy subjects [119, 139] and 90% of VO_{2peak} in patients [120-122] has been demonstrated to be more beneficial than lower intensities. Also in COPD patients the physiological effects of training are demonstrated to be greater in those who are able to train at higher intensities compared to

lower intensities [108, 113, 130, 140-143]. Many low and moderate intensity studies demonstrate nonsignificant increases or even decreases in VO_{2peak} and performance after training [144-148]. It has also been demonstrated that oxidative enzymes of peripheral muscles increases only after high intensity training and not after low intensity training [149]. Exercise capacity is severely compromised in COPD because of ventilatory limitation [78, 150] and due to the increased work of breathing and muscular symptoms during exercise, high intensity training (>70% of peak work load) are hardly tolerated for longer periods of time [108, 109, 113]. As common training intensities in COPD is moderate (<70% of peak work load) to be able to sustain trainig duration (~30 min), heart rate will not be desirable challenged and the muscle oxygen diffusing capacity might not reach its potential maximal value during exercise [9]**.** Muscle biopsies have demonstrated increases in the levels of aerobic enzymes and capillary density of leg muscles after high intensity training in COPD patients [107, 109].

1.9 Interval training

Interval training consists of intermitted work alternating with active rest. In athletes and healthy older subjects, interval training increase VO_{2max}, work load and lactate thresholds to a greater extent than continuous low to moderate intensity training [151-153]. Aerobic high intensity interval training performed by 4x4 minutes at 85-95% of maximal heart rate intermittet by 3 minutes at 60-70% of maximal heart rate has demonstrated significantly improved VO_{2max} and peak work load compared to continues training at lower intensities (< 70-75 % of maximal heart rate) in healthy young subjects [119, 154, 155] and sedentary elderly adults [156].

In COPD patients, ventilation constrain exercise tolerance due to rapidly developing hyperinflation and dyspnoea, thereby increased intensity is hardly sustained [78].
As the working periods is intermittent with resting periods, high intensity is better tolerated in COPD patients during interval training [75, 99, 157] and they are able to perform a greater amount of work than during continuous exercise [158, 159]. Thereby interval training elicits great training responses at a reduced ventilatory level by a delayed onset of dynamic hyperinflation and dyspnoea which allows a greater opportunity for exercise progression [38, 78, 150]. However, as several studies on healthy and diseased people have demonstrated great increases in $VO_{2max/peak}$ by performing 4 x 4 minutes intervals at 85-95% of peak heart rate [54, 119-122], interval periods used in most COPD studies last from 20 seconds to 1 minute at

90-100% of peak work load [131-133, 159]. In these studies, an increased performance is demonstrated by increased quality of life, work load and/or walking distance, but without significant increase in VO_{2peak}. However, as the intensity in therse studies is near maximal work loads, an increase in VO_{2peak} is not expected. One study of COPD patients performing 3 minute intervals 2 times pr week for 16 weeks at >80% of peak work load demonstrated increased VO_{2peak}, but the increase was only about 5% [126].

1.10 Reduced muscle mass

Isolated small muscle mass exercise and one leg cycling has demonstrated greater muscle mass specific power output and stimulus than whole body exercise in COPD patients, potentially leading to a greater training response [40, 94, 128, 160]. In healthy people, leg blood flow and leg VO_{2peak} increases during one leg cycling compared to two legs cycling where an increased vascular resistance causes a reduced blood flow to the working muscles and reduces oxygen delivery/diffusion [161, 162]. The respiratory muscles demand about 14-16% of cardiac output during heavy exercise [163], whereas during reduced muscle mass exercise, central components are less taxed resulting in increased vascular conductance and blood flow, allowing a greater level of skeletal muscle perfusion to be achieved [164-166]. As a greater proportion of the blood is directed to the isolated area, VO_{2peak} in the isolated quadriceps muscle group is demonstrated to be 2-3 times higher than measured in the same muscle group during whole-body work [45, 167].

For individuals with impaired lung function, the added demand for rapid gas exchange in whole-body work with increased intensity might result in exercise cessation. This is due to the increased cost of breathing as demonstrated by loaded respiratory muscle reducing VO_{2max}, performance and leg blood flow, as a consequence of blood redistribution away from the locomotor muscles and vasoconstriction compromising perfusion [38, 163, 166]. Increased inspiratory muscle work may contribute to dyspnoea and exercise limitation even before the ventilatory ceiling is attained [157, 168]. During small muscle mass exercise like one leg cycling, sufficient oxygen rich blood is allowed to supply the working muscles without any competition from other muscles which in turn facilitate the ventilatory work and increases the blood flow [38, 99]. This increases the ability for ventilatory limited patients to sustain the high intensity training and thereby recruit their maximal muscle conductance. This strategy has been found to increase VO_{2peak} by~20% in COPD patients performing 15 minutes one by one leg cycling [128].

1.11 Training and testing in hyperoxia

Oxygen diffusion from air to blood is a product of the partial pressure difference of oxygen between alveolar air and capillary blood and depends on alveolar ventilation and capillary perfusion, the alveolar and capillary surface areas, haemoglobin content and membrane thickness [169]. Oxygen supply to the skeletal muscle is a function of the arterial oxygen content and muscle blood flow [170]. Hyperoxia is defined as an inspiration of a gas mixture with an oxygen content exceeding ambient air and has at maximal exercise demonstrated increased arterial oxygen saturation [37, 171, 172] and performance in endurance athletes [43, 173, 174] as well as in healthy and untrained subjects [37, 42, 175].

In COPD patients, ventilation/perfusion fails to keep pace with oxygen consumption causing an increased dead space [18] and reduced arterial oxygen saturation [79, 176]. Oxygen acts a dilator in the pulmonary circulation [177] whereas it might be a vasoconstrictor in vascular beds in both healthy [172] and COPD patients [178]. However, a higher oxygen content in the arterial blood by breathing supplemental oxygen overbalances the vasoconstrictor effect of oxygen [179] on the microvasculature and might thereby improve exercise tolerance by improving peripheral oxygen saturation and delivery [39, 110, 180]. Hyperoxia during aerobic exercise training in COPD patients has been demonstrated to improve exercise tolerance, performance and respiratory muscle function [181] due to relief of the ventilatory work and dyspnoea by a decreased stimulation of the chemoreceptors in the carotid and aortic bodies [182], relief of pulmonary vasoconstriction and decreased ventilatory rates [183] resulting in a reduced ventilatory requirement for a given exercise [39, 182, 184-188]. Thereby the respiratory or cardiovascular system is required to do less work, or to work more efficiently at a given work load [176]. Long term hyperoxia may induce pulmonary vasodilatation and improve right heart function [189].

The increased oxygen pressure increases arterial oxygen saturation in the blood and thereby systemic oxygen delivery which increases the “driving force” for oxygen diffusion into the muscle [129, 190]. Together with increased blood flow in hyperoxia [39], this might in turn increase limb muscle oxygen utilization and enable the exercising muscles to perform more external work, which has been demonstrated to increase the physical performance because it allows for higher training intensity [127] and might elicit shear stress. Hyperoxia has also been found to improve skeletal muscle electrical activity during dynamic exercise [191].

Even though hyperoxia increases intracellular partial pressure of oxygen and thereby VO_{2peak} [39, 127], this relationship is not constant as it has been demonstrated an increased performance in hyperoxia compared to normoxia without any difference in VO_{2peak} [188], indicating a borderline in terms of supply limitation [192, 193].

Acute hyperoxia during peak exercise might reveal the contribution of factors limiting VO_{2peak}. Increased VO_{2peak} in acute hyperoxia compared to normoxia indicate a limitation by the cardiovascular system to supply the working muscles with oxygen in normoxia, whereas no difference in VO_{2peak} between hyperoxia and normoxia indicate a demand limitation in the muscles to consume oxygen. Due to special required equipment, not many studies have measured hyperoxic VO_{2peak}. However, acute hyperoxia during whole body cycling and one legged knee-extension in patients with COPD has demonstrated a metabolic reserve capacity during whole body work by an increased performance in hyperoxia compared to normoxia [40]. A subsequent study documented that the greater work capacity of the lower limbs in hyperoxia was accompanied by increases in oxygen delivery and oxygen uptake in the leg [39], which indicate that the metabolic capacity of the lower limb muscles to consume oxygen was not exhausted in COPD patients in normoxia. A few studies both on healthy subjects and COPD patients have demonstrated that inspiration of oxygen enriched air during whole body and small muscle group exercise did not increase performance or VO_{2peak} despite increased tissue oxygen diffusion driving pressure [129, 194, 195]. This suggests a peripheral limitation to VO_{2peak} which may relate to the reaching of a ceiling for maximal mitochondrial oxygen turnover.

1.12 Work economy

Work economy is defined as oxygen cost at a standardized workload and refers to the ratio between work output and energy input. It establishes the relationship between maximal steady-state VO_2 and work up to the lactate threshold level. Endurance capacity is dependent upon work economy and lactate threshold in addition to VO_{2peak} , whereas work economy influences the work rate at VO_{2peak} [17]. This might result in increased peak work load without any increase in VO_{2peak} due to the reduced oxygen cost to perform the same work pre and post training. Reduced mechanical efficiency has been demonstrated in COPD patients, and is defined as the precentage of total energy expended that contributes to external work, with the remainder lost at heat [196]. This seems to be related to muscle fibre type composition with reduced muscular oxidative enzyme activity, metabolism and muscle

capillarization in addition to physical inactivity [11, 94, 98, 197, 198]. It has been established that high intensity endurance training improves submaximal exercise performance in COPD patients [199]. Maximal strength training improves work economy due to an elevated rate of force development and increased maximal strength demonstrated by working at a relative lower percent related to 1RM at the same work load pre and post training [200, 201]. As previously discussed there is a growing reliance upon type II muscle fibres as exercise intensity increases in COPD. The type II muscle fibres have been proposed leading to less efficient muscular work. Fibre type changes and subsequent fibre type recruitment may explain the decreased mechanical efficiency in these patients [94].

1.13 Quality of life

COPD has a negative impact on health related quality of life [75], but improves as a result of increased exercise capacity after rehabilitation [100, 126, 199, 202-205]. Improvements in quality of life seem to be related to an improvement in work economy and an increased VO_{2peak} accompanied by aerobic high intensity training [120, 199, 206]. Thereby comparable changes in health related quality of life and exercise capacity in COPD patients following aerobic interval training has been identified [131, 132].

2 Objective, aims an hypotheses of the studies

The main focus of the present thesis was to explore new and improved aspects of endurance training for patients with chronic obstructive pulmonary disease, and to investigate whether peak oxygen consumption are primarily limited by the reduced pulmonary function and thereby the capacity to transport oxygen to the working muscles or by the muscles capacity to utilize the available oxygen.

Paper I: Aerobic high intensity one and two legs interval cycling in Chronic Obstructive Pulmonary Disease; the sum of the parts is greater than the whole

The aim of the study was to to assess the impact of aerobic high intensity interval training in COPD patients and reveal whether this training modality performed using individual leg cycling could produce a higher whole body training response than two legs cycling.

It was hypothesised that;

> Aerobic high intensity one leg interval cycling will maximally challenge the peripheral muscles without gaining a ventilatory limitation, and thereby result in a significantly greater whole body VO_{2peak} training response than aerobic high intensity two legs interval cycling.

Paper II: Aerobic high intensity one leg interval cycling improves peak oxygen uptake in Chronic Obstructive Pulmonary Disease patients; no additional effect from hyperoxia

The aim of the study was to address whether hyperoxia during high intensity aerobic interval one leg cycling in COPD patients show additional training effects on VO_{2peak} compared to ambient air, in addition to exploring the acute exercise limitations.

It was hypothesised that;

1. COPD patients performing aerobic high intensity one leg interval cycling in hyperoxia will increase VO_{2peak} and performance more than those training in normoxia due to the increased driving force of oxygen into the mitochondria.

2. If a metabolic reserve capacity exists in the muscles to consume oxygen pre and post training, it will be revealed by increased VO_{2peak} in acute hyperoxia compared to normoxia as more oxygen is available in the vascular bed.

Paper III: Hyperoxic interval training in chronic obstructive pulmonary disease patients with oxygen desaturation at peak exercise

The aim of the study was to address if hyperoxia during whole body training in COPD patients with oxygen desaturation at peak exercise (SpO_2 < 88%) increase VO_{2peak} and performance more than in normoxia. This might be due to an increased oxygen delivery/diffusion into the muscles which allow the patients to maintain the high intensity metabolic muscular work.

It was hypothesised that

1. Hyperoxia during aerobic high intensity interval training in COPD patients with oxygen desaturation at peak exercise allows the patients to sustain the preferable high training intensity and increase the driving force of oxygen into the working muscles which will result in a great improvement in VO_{2peak} and performance pre to post training.
2. Acute hyperoxia at pre and post test will increase VO_{2peak} and performance compared to normoxia due to the oxygen supply limitation in normoxia.

3 Methods

3.1 Subjects

37 COPD patients and 8 coronary artery disease (CAD) patients was included in the present thesis (Table 1). Inclusion and exclusion criteria are described in detail in the papers.

19 COPD patients completed the study described in paper I, 12 in the one leg group and 7 in the two legs group. In study II described in paper II, 7 and 5 COPD patients completed the one leg training intervention in hyperoxia and normoxia respectively. In study III described in paper III, CAD patients who did not oxygen desaturate at peak exercise were used as controls to compare the hyperoxic stimuli during training and acutely during testing in subjects with a different disease and thereby physiological condition.

Table 1 Overview of the subjects included in the thesis and the inclusion criteria in each study.

	Number of patients		Inclusion criteria		
	Intervention		COPD		CAD
Paper	1	2	GOLD stage	additional criteria	Angina pectoris class
I	12 COPD	7 COPD	III	-	-
II	7 COPD	5 COPD	III	-	-
III	6 COPD	8 CAD	III	exercise SpO_2 < 88 %	I-III

COPD; chronic obstructive pulmonary disease, CAD; coronary artery disease, GOLD stage III; FEV_1 between 30 - 50% and FEV_1/ FVC < 70% of predicted value, SpO_2; arterial oxygen saturation, Angina pectoris classification see Braunwald et al. [207].

3.2 Testing procedures

The pulmonary function tests were performed at the hospital by research nurses. All physical exercise capacity tests were performed in the exercise physiology laboratory at the hospital area, organized and accomplished by two exercise physiologists and supervised by a medical doctor.

3.2.1 Spirometry

Flow volume Spirometry measurements were performed at room temperature (20 to 22°C) with the Master Screen pneumo Spirometer, version 4.1 (Jaeger GmbH & Co KG). The spirometer was calibrated daily, and the better of two post bronchodilator measurements with < 5% variation was recorded. The tests were performed at approximately the same time of day, and there were no change in medication during the studies.

3.2.2 Work economy

In study III, work economy at a work load corresponding to 20 and 40 watt in the COPD and the CAD group respectively during treadmill walking was measured. The COPD patients performed the test at 20 watts due to their severe condition. Oxygen uptake in each subject was divided by 20 and 40 watts in the COPD and the CAD group respectively so that they were comparable. To define the walking speed which corresponded to 20 watts and 40 watts on the treadmill the following equation was used:

$$V = \frac{workload}{[m_b \cdot g] \cdot \sin(\theta)} \cdot 3.6 \qquad (2.1)$$

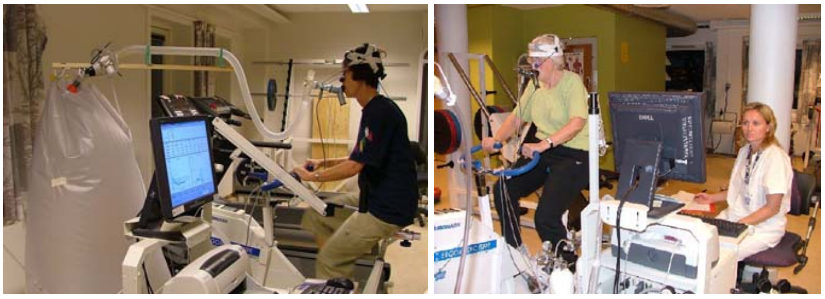
V = velocity [km $\cdot h^{-1}$]
Work load = 20/40 Watt [Nm $\cdot s^{-1}$]
g = gravitational constant [9.8 m $\cdot s^{-2}$]
m_b = body mass [kg]
θ = treadmill inclination [deg]
3.6 = converting velocity expressed [m $\cdot s^{-1}$] into [km $\cdot h^{-1}$]

Oxygen uptake was determined by measuring 5 minutes continuous respiration, and defined as the mean oxygen uptake at the three latest 10 sec measurements.

3.2.3 Peak oxygen uptake

VO_{2peak} was determined by increasing the work load until the subjects reached exhaustion. Continuous respiratory measurements were carried out and the mean of the three highest 10 seconds continuous respiratory measurements determined VO_{2peak}. In study II and III the Sensormedics V-max spectra 229 analyzer (Sensormedics Corp, California, USA) was used in

respiratory measurements due to the hyperoxia testing, and in study I Cortex Metamax II portable metabolic test system (Cortex Biophysic GmbH, Lepzig, Germany) was used to obtain respiratory measurements.



(a) (b)

Fig. 1 Incremental peak exercise testing performed by two legs cycling while breathing supplemental oxygen (a) and ambient air (b).

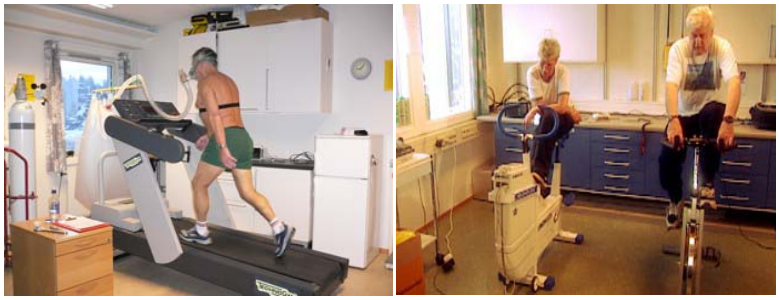
In study I and II the subjects cycled on an ergometer bike (Electronic Ergomedic 839E, Monark Exercise AB, Sweden). Work load was gradually increased until the subjects reached exhaustion. In study III VO_2 was measured during treadmill walking (Technogym runrace, Italy) and the work load was increased either by speed or inclination until the subjects reached exhaustion. To decide VO_{2peak} the mean of the three highest 10 second continuous oxygen uptake measurements were used.

In study III the subjects tested work economy and VO_{2peak} both in normoxia and in hyperoxia (65% oxygen which were the highest amount of oxygen the analyzer could measure). The two tests were performed in a random order separated with at least a 24 hour rest period.

3.3 Training procedures

In all studies the training intervention performed were aerobic high intensity interval training either by two legs cycling (I), one leg cycling (I and II) or treadmill walking (III). The subjects trained in normoxia (I and II) and in hyperoxia (II and III) in a total of 24 training sessions. The hyperoxia training was performed during one leg cycling (II) and treadmill walking (III) by breathing oxygen through a face mask with a three way valve connected to a 200 litres plastic bag, constantly refilled with 100% oxygen from a gas reservoir tank.

After 5-10 minutes cycling or walking at the intensity comfortable for warm up, patients performed 4 x 4 minutes of aerobic high intensity intervals at 85-95% of the individual patients' peak heart rate, corresponding to 80-90% of VO_{2peak}. 3 minutes of active rest periods (60-70% of VO_{2peak}) were used in-between the working periods in study I (TLT) and III whereas in study I (OLT) and II the subjects switched between the two legs, allowing one leg to rest while the other was working.



(a) (b)

Fig. 2 Aerobic high intensity interval training performed by treadmill walking while breathing supplemental oxygen (a) and one and two legs cycling while breathing ambient air (b).

Training intensity was chosen after documentation of the superiority of the aerobic high intensity training compared to moderate intensity training in healthy individuals and patients [119-122] and calculated as % of peak heart rate, peak work load and VO_{2peak} obtained at the pre training test [208]. Heart rate together with the Borg rating scale for perceived exhaustion was used to control the intensity during each training session. The training load was increased whenever the heart rate or the Borg rating score decreased under the desired level during the intervals. The use of heart rate as a predictor to set the training intensity in COPD patients has been found reliable together with the use of dyspnoea ratings [75, 209-212]. All training sessions were supervised by an exercise physiologist to ensure training quality and performed in immediate nearness to the Hospital and a pulmonary doctor to ensure safety.

3.4 Quality of life

Quality of life was measured by the short form 36 questionnaire (SF-36), consisting of questions concerning self-percepted physical and mental health status. The SF-36 questionnaire is a multi-purpose short-form health survey, which measures medical status and outcome after interventions and is a generic measure, as opposed to one that targets a specific

age, disease, or treatment group. It has been found valid to use on COPD patients [213, 214] and has proven useful in surveys of general and specific populations, comparing the relative burden of diseases, and in differentiating the health benefits produced by a wide range of different treatments. Patients filled in identical questionnaires pre and post the intervention.

3.5 Statistical analysis

Statistical analyses were performed using the software SPSS, version 11-13 (Statistical Package for Social Science, Chicago, USA). Table values are expressed as mean ± standard deviation (SD) and as mean (range), while figure values are expressed as mean percentage change and data variability as standard deviation (SD) or standard error (SE). A two-tailed p value < 0.05 was accepted as statistically significant for all tests. Due to relatively small sample size in all studies, non parametric statistics were chosen for the analyses. Between groups differences was tested using the Mann-Whitney U test on delta values from pre to post test while within group changes from pre to post test and differences between normoxia and hyperoxia was tested using the Wilcoxon signed-rank test.

4 Summary of results

Paper I: Aerobic high intensity one and two legs interval cycling in Chronic Obstructive Pulmonary Disease; the sum of the parts is greater than the whole

1. Whole body VO_{2peak} and peak work load increased by 12 and 23% in the one leg training group (OLT) and by 6 and 12% in the two legs training group (TLT) from pre to post training respectively.

2. The increase in whole body VO_{2peak} and peak work load pre to post training was significantly greater in the OLT than the TLT.

3. One leg VO_{2peak} and peak work load increased by 18 and 37% from pre to post training in the OLT.

Paper II: Aerobic high intensity one leg interval cycling improves peak oxygen uptake in Chronic Obstructive Pulmonary Disease patients; no additional effect from hyperoxia

1. One leg VO_{2peak} increased in the Hyperoxia training group (HTG) and the Normoxia training group (NTG) by 24 and 15% respectively whereas peak work load increased by 31 and 36% in the two groups respectively, from pre to post training, with no differences between groups.

2. Whole body VO_{2peak} increased in the HTG and the NTG from the one leg training by 14 % whereas peak work load increased by 20 and 22% in the two groups respectively, from pre to post training, with no differences between groups.

3. No significant difference in VO_{2peak} between normoxia and acute hyperoxia at pre or post test in the HTG were found even though arterial oxygen saturation was significantly higher in hyperoxia at all occasions, pre and post one and two legs, by 5, 5, 4 and 6% respectively.

Paper III: Hyperoxic interval training in chronic obstructive pulmonary disease patients with oxygen desaturation at peak exercise

1. VO_{2peak} and peak work load increased by 19 and 75% respectively in the COPD group and by 15 and 30% respectively in the CAD group from pre to post training.
2. In the COPD group, VO_{2peak} and peak work load was significantly higher in acute hyperoxia compared to normoxia at pre test by 20 and 32% respectively and at post test by 14 and 26% respectively.
3. Arterial oxygen saturation was significantly higher (13%) in hyperoxia compared to normoxia at pre and post test.
4. Work economy was 10% improved in the COPD and CAD group form pre to post training.
5. Quality of life was improved in the COPD group in both self-percepted physical and mental health status by 24 and 35 % respectively.

5 Discussion

The present thesis demonstrates that aerobic high intensity interval training at 85-95% of peak heart rate increases VO_{2peak} and peak work load in patients with severe COPD in different types of exercises such as regularly cycling (I), one leg cycling (I, II) and treadmill walking (III). Hyperoxic training is an advantage in whole body work in patients with hypoxemia (SpO_2 < 88%) during exercise. The one leg cycling training was superior to the two legs cycling training (I). One leg cycling was more efficient when measured as % improvement pre to post training compared to two legs cycling in normoxia and hyperoxia (II), and treadmill walking in hyperoxia (III). Patients without hypoxemia during exercise (I-II) were mainly demand limited by the skeletal muscles capacity to consume oxygen before and after the training intervention. Hyperoxic patients during exercise (III) were limited by the capacity to supply oxygen to the skeletal muscles in both the untrained and trained state.

5.1 Increase in peak oxygen uptake

5.1.1 Training using reduced muscle mass vs. whole body work

5.1.1.1 Central and peripheral stimuli

In the present thesis, one leg cycling (I, II) increased whole body VO_{2peak} by 12-14% which were significantly more than two legs cycling with an increase of 6% pre to post training (I). This demonstrates the importance of a high intensity performance at the muscular level during training. It has been demonstrated that COPD patients are able to perform almost four times more work during one leg exercise compared to two legs exercise, and lower ventilation allows the patients to exercise longer at the same muscle specific intensity [160]. One leg cycling allows the patients to train at a higher muscle specific intensity compared to whole body exercise as the ventilatory load is relatively reduced and skeletal muscle blood flow is increased [166], thereby greater training responses is revealed. The present findings from the one leg training (I, II) is supported by a recent study of COPD patients [128]. After 7 weeks of high intensity training, cycling with each of both legs at 50% of two legs peak work load for 15 min increased VO_{2peak} in the one leg cycling group by 20%. However no significant change in VO_{2peak} in the two legs group which trained continuous cycling for 30 min at 70% of peak work load was found. These results indicate that one leg cycling enhances the adaptive response of peripheral muscle more than conventional two legs cycling.

In the present thesis, VO_{2peak} and peak work load were significantly increased both in one and two leg cycling after one leg training (I). However one leg VO_{2peak} increased more than whole body VO_{2peak} after one leg cycling, which indicates a central limitation to whole body work in these COPD patients. The ability to consume oxygen by the peripheral muscle before the training intervention was stressed to the limit during one leg cycling, and since the work performed one by one leg was greater than when working together, the patients had a peripheral muscle reserve capacity when performing two legs cycling. These findings appeared even clearer after the training intervention as the difference between one and two legs VO_{2peak} were smaller which indicate that the peripheral muscle capacity was relatively more improved than the central factors. One leg VO_{2peak} was about 60 % of two legs VO_{2peak} at pre test whereas at post test the one leg VO_{2peak} was about 80 % of two legs VO_{2peak} which suggests an increase mainly attributed to the peripheral muscle level. The less improved VO_{2peak} in two legs cycling might be explained by that locally improved aerobic endurance training, here represented by one leg cycling, might be of less advantage in exercise with large muscle mass if the central circulation is not equally improved. This is in line with others who have demonstrated reduced whole body VO_{2peak} compared to one leg VO_{2peak} after training each leg separately [45, 161, 167]. Training with one leg in healthy people has been demonstrated not to represent a sufficient stimulation of the central circulation to produce an improvement of cardiac function as it is emphasized that large muscle groups must be engaged to induce central circulation [215]. Peak heart rate was unaffected by training (I,II), similar to the study by Klausen et al. [161] and was during peak one leg cycling about 90% of peak two legs cycling, thereby the cardiovascular system was not maximally challenged during the one leg cycling and the training was well tolerated by the patients. However as the peak heart rate during two legs cycling did not differ between pre and post test with a significantly greater VO_{2peak} and peak work load, a certain central training adaptation most likely occurred after the one leg training (I, II). The findings in study I indicated a central limitation in the ability to supply the working muscles adequately with oxygen when attending whole body exercise. This is in accordance with findings of Richardson et al. [40] who compared single leg knee extensor exercise with stationary two legs cycling and found that patients with COPD were able to exercise at a higher muscle specific intensity during single leg extensor exercise compared to conventional cycling. Their findings indicated a metabolic reserve in the exercising muscle when the patient terminared two legs exercise. Training with reduced muscle mass has given evidence in favour of an increased portion of cardiac output to

the working muscles, because the capacity of the cardiovascular system is not taxed maximally, both in healthy and in COPD patients [40, 43]. Thereby a relatively greater training adaptation might have occurred in the peripheral muscles compared to the central factors leading to an imbalance which might result in a peripheral reserve capacity during whole body work in COPD patients.

Similar to the findings in study I, study II demonstrated a reduced training response in whole body VO_{2peak} compared to one leg VO_{2peak}. Thereby we attend towards the "peripheral muscle reserve capacity during whole body work" theory as in study I. However, in study II it was also demonstrated that acute hyperoxia did not increase VO_{2peak} above the level found in normoxia during whole body work, even though arterial oxygen saturation per see was increased. This finding indicated an oxygen demand limitation in the peripheral muscles to utilize the increased arterial oxygen saturation. Even though arterial oxygen content is increased, we do not know if the oxygen content in the peripheral vessels is equally increased or if the oxygen cascade from the arteries to the periphery is significantly decreased. Central factors such as the respiratory work, cardiac output and blood flow might limit the performance in whole body work compared to one leg work which might also count for an central limitation to supply the peripheral muscles with oxygenated blood [38]. As the ventilation is equally high during peak one and two legs cycling, a reasonable explanation for the reduced increase in whole body work compared to one leg is a ventilatory limitation to perform whole body work in patients with COPD due to a ventilatory ceiling which results in a termination of work before the peak capacity is reached in the peripheral muscles. If that is the case, increased oxygen content in the periphery would not be of any importance.

5.1.1.2 Ventilation

The ventilation/VO_2 relationship were constant and independent of the muscle mass involved during testing (I, II). However, as the VO_{2peak} during one leg cycling were significantly lower than the VO_{2peak} during two legs cycling, one leg cycling requires lower ventilation than two legs cycling at the same relative work load. Thereby, if there is a ventilatory ceiling when concerning high intensity training in COPD patients, training with a reduced muscle mass allows for a higher relative work load compared with whole body work. As illustrated in figure 1 in paper I, a significantly lower training work load in the one leg group compared to the two legs group was found during the first two weeks of the training intervention. However, from week 3, the work load was not different between the groups in which the one

leg group trained at the same work load as the two legs group, by cycling with each of both legs separately. During the last week of training, the one and two legs group actually trained at the exactly same work load by cycling with one leg at a time and two legs together respectively. The reduced pulmonary function of patients suffering from COPD indirectly influences the intensity and thus training stimulus negatively due to the heavy work of breathing and dyspnoea during whole body aerobic high intensity interval training. It is suggested that in COPD patients, blood flow directed to the peripheral muscles and oxygen extraction may be limited due to a redistribution of cardiac output and oxygen from the peripheral working muscles to the ventilatory muscles [38]. This is demonstrated by the greater increase in VO_{2peak} after the one leg cycling training period when the lungs are less challenged at the same relative muscle specific intensity (I, II). As demonstrated in the study by Harms et al. [166], respiratory work during maximal exercise caused changes in locomotor muscular resistance and perfusion, and thereby directly changed VO_2 in the leg. In addition these changes were greatest when the ventilatory work was increased. A redistribution of cardiac output from the locomotor muscles to the ventilatory muscles limits blood flow and oxygen extraction during whole body work [38]. Thereby as training with an isolated muscle mass relatively reduces the work of breathing, oxygenated blood is directed to the working skeletal muscles. This will allow the patients to work at a higher muscle specific work load before they reach the ventilation limitation. As demonstrated in study I and II the peak work load performed by one leg alone was about 60 and 80% of the sum of the two legs work load together at pre and post test respectively, giving a greater peripheral muscle stimulus during one leg training. These findings are in line with the study by Dolmage et al. [160] who demonstrated that the COPD patients during single leg exercise were able to perform 80% of the power output performed during two legs cycling suggesting that the exercising muscle was not maximally stressed during two legs exercise. Reduced ventilation has been reported to increase blood flow [163, 166] and thereby more oxygenated blood might have been distributed to the mitochondria available for energy transfer. It has been demonstrated that after a training period, leg blood flow increases during one leg exercise, but decreases during two legs exercise [161]. As more blood is distributed to an isolated area during the one leg work, it induces shear stress to the vessels. To alleviate this increased shear stress structural changes occurs [216]. Since leg vascular resistance decreases during one leg exercise, VO_{2peak} per unit tissue depends on the muscle mass involved [161]. A vascular constriction during two legs cycling could have attributed to the reduced training stimulus (I) and to the small difference between one and two legs VO_{2peak} and peak work load (I, II). It has been

demonstrated that involving a larger muscle mass into the work induces vasoconstriction in the periphery and subsequently reduces leg VO_{2peak} and blood flow to the peripheral muscles [162, 217-219].

5.1.2 Training responses in normoxia vs. hyperoxia

In study I, the one leg training revealed great changes pre to post training in both one and two legs VO_{2peak} by 18 and 12% respectively, and peak work load by 37 and 23% respectively. The increases in VO_{2peak} and peak work load were greater from the one leg training compared to the two legs training which increased VO_{2peak} and peak work load by 6 and 12% pre to post training respectively. This difference was found to be due to an increased peripheral stimuli during the one leg training, and thought be attributed to the increased blood flow and oxygen delivery to the peripheral skeletal muscles, and thereby the oxygen availability in the mitochondria. A further increase in VO_{2peak} and peak work load by performing the exact same training intervention in hyperoxia was thereby hypothesised to reveal even greater training responses in study II due to further increased oxygen availability in the peripheral muscles. In all studies of the present thesis (I-III), both during one and two legs cycling, arterial oxygen saturation was significantly higher in hyperoxia compared to normoxia. The increased arterial oxygen saturation is hypothesised to increase oxygen delivery to the periphery and thus increase the peripheral muscle stimulus. However, aerobic high intensity interval one leg cycling in hyperoxia had no additional effect compared to the same training intervention in normoxia when concerning increased VO_{2peak} from pre to post training (II). This finding is supported by others who have found no additional effect of hyperoxia during training, however one of the studies did not find any increase in VO_{2peak} either by breathing ambient air or supplemental oxygen [129] and the other study did not measure VO_{2peak} [195]. Both studies consisted of whole body exercise. Several factors might explain lack of improvement in VO_{2peak} in hyperoxia compared to normoxia in study II. Hyperoxia was adopted to increase the oxygen content and thereby oxygen pressure in the capillaries leading to an increased energy transfer and power output at the muscular level. Arterial oxygen saturation was significantly increased in hyperoxia compared to normoxia in the COPD patients in both the hyperoxic studies (II-III). In spite of these differences, similar improvements in VO_{2peak} by training one leg cycling in normoxia and hyperoxia in study II was found. A plausible explanation could be that during one leg cycling training the ventilatory system was relatively less stressed, thereby the blood was already distributed to the periphery. Due to the reduced muscle mass, the continuously presence of a greater blood flow with oxygenated blood in the

working skeletal muscles induced satisfactory stimulation on the peripheral muscles allowing a maximal metabolic muscular work even in normoxia. Richardson et al. [35] demonstrated that hypoxemia during exercise resulted in increased blood flow and a greater oxygen extraction in the tissues without any change in VO_2. It is thereby reasonable to believe that blood flow is regulated by arterial oxygen content and muscle oxygen demand. One leg cycling did not induce oxygen desaturation at peak exercise, thereby it is reasonable to anticipate a satisfactorily maintained oxygen saturation during the training sessions in normoxia as well (I, II).

As demonstrated in study II, non hypoxemic COPD patients significantly decreased ventilation by 12% and increased work load by 13% during peak two legs cycling in hyperoxia compared to normoxia both pre and post training. This is in line with others demonstrating that hyperoxia might reduce ventilation and result in a higher muscular specific training intensity in those without hypoxemia at peak exercise [180, 182, 186-188, 195]. However during one leg peak cycling, ventilation and work load was not different between hyperoxia and normoxia. Thereby the finding that hyperoxic one leg cycling training did not increase VO_{2peak} above the level attained by normoxic training after eight weeks of aerobic high intensity interval training is not incomprehensible. As ventilation, blood flow and oxygen saturation might be optimal during the one leg cycling condition, even in normoxia, the effect of hyperoxia in a contrary situation was investigated in study III. The response of hyperoxia during aerobic high intensity interval treadmill walking in patients with hypoxemia during peak exercise was revealed. Findings from study III demonstrated greater increase in VO_{2peak} (19%) compared to studies I and II (6, 12 and 14%). In study III, a significant higher VO_{2peak} and peak work load in hyperoxia compared to normoxia at pre and post test was found, however without any difference in ventilation. This indicate that exercise hypoxemic COPD patients is able to sustain a higher intensity at the same relative ventilation in hyperoxia compared to normoxia, resulting in great improvements in VO_{2peak}. Several studies have demonstrated an improved performance and ventilation in hyperoxia compared to normoxia in both those with mild resting hypoxemia, hypoxemia during exercise [186, 220] and in those without hypoxemia during exercise [127, 180, 182, 184, 187, 221]. An important fact in the present thesis is that the patients in study III were the patients most afflicted by the disease with the lowest pulmonary functions and the lowest initial fitness status which may account for larger relative improvement in VO_{2peak} [113, 215].

As demonstrated in the present thesis (I) and by others, one leg cycling in normoxia gives a great opportunity to induce optimized training conditions in the peripheral muscles. This is due to that the respiratory muscle work is relatively reduced and the blood flow and oxygen saturation increased [161, 162], which induces only small differences in hyperoxia (II). In whole body work however, central factors such as respiratory muscle work, cardio vascular vasoregulation and arterial oxygen saturation influences to a greater extent the performance, thereby the hyperoxic responses is much more evident. This is evidenced by larger improvements in VO_{2peak} after hyperoxic treadmill walking (III) (19%) than after normoxic two legs cycling (I) (6%). It is also evidenced by increased VO_{2peak} in hyperoxia compared to normoxia (III). Thereby it is not surprising that whole body exercise in study I and III demonstrated the most different results when concerning the physiological training effects from pre to post training. Patients who walked at the treadmill, oxygen desaturated at the training intensity level and had their arterial oxygen saturation restored in hyperoxia. The two legs cycling group also had reduced arterial oxygen saturation during training, however they were not hypoxemic ($SpO_2 < 88\%$). As the treadmill hyperoxic training group demonstrated 19% increased VO_{2peak} compared to the 6% in the cycling normoxic training group, possible parameters other than oxygen availability in the muscle might have contributed to limit the performance in the whole body work. It seems from the one leg interventions (I, II) that a ventilation ceiling might contribute to exercise limitation before the skeletal muscle reaches its limitation during whole body work. Thus the relatively reduced ventilation induced by breathing oxygen in study III might have redistributed blood to the locomotor muscles which allowed the treadmill group to train at a higher peripheral skeletal muscle specific intensity than the two legs cycling group in study I. Thereby the treadmill group might have increased the training intensity at a faster rate than the normoxic group. This assumption is supported by the findings of others [127, 195] demonstrating that during training in hyperoxia, intensity could be kept at a higher level resulting in improved endurance capacity and breathing pattern compared to normoxia. Even though the two legs cycling group (I) were not hyperoxic, a reduction in arterial oxygen content at peak exercise was present and might have been determining as the blood flow is decreased in whole body work and thereby the oxygen availability might be reduced.

5.1.3 Stationary cycling vs. treadmill walking

When comparing percent increase in whole body VO_{2peak} from pre to post training in studies I-III, treadmill walking in hyperoxia (III) had the greatest improvement in VO_{2peak} which was

three times the improvement found after the two legs cycling (I), by 19 and 6% respectively. One leg cycling (I-II) came next to the hyperoxic treadmill exercise with an increase in whole body peak exercise of 12 and 14% respectively, while two legs cycling (I) increased the least after performing the same training intervention, aerobic high intensity interval training. Even though inclined treadmill workout has been found to induce 10-20% better performance during walking and running compared to stationary biking [32], the subjects trained and tested at the same physical device pre and post training and should therefore not be affected by these differences. Ergometer cycling was chosen as intervention to compare reduced muscle mass training with whole body training (i.e. one and two legs cycling). Treadmill walking was chosen in study III as the aim was to investigate the hyperoxic response in a condition where normoxia probably would limit exercise and maximally challenge the oxygen delivery/availability issue. During treadmill walking, a greater muscle mass is required and reveals greater ventilatory requirements compared to stationary cycling [222, 223]. As treadmill walking induces performance to a greater extent than cycling [32], the greater increase in VO_{2peak} from the treadmill study (III) might be explained by a greater training adaptation in the cardiovascular system in addition to the peripheral skeletal muscles, than seen in the cycling studies (I, II).

5.2 Limitations to VO_{2peak}

Hyperoxia significantly increased arterial oxygen saturation compared to normoxia at peak exercise in both one and two legs cycling at pre and post test in the COPD patients (II, III) by 4-13%. The greatest increase was found in study III by a 13%, not surprisingly as these patients were hypoxemic at peak exercise in normoxia. Increased arterial oxygen saturation demonstrates improved oxygen availability in the arteries during activity. The results from the present studies (I-III) lay the foundation for further investigation into the mechanisms behind the oxygen content in the peripheral vascular bed and blood flow in COPD patients as these parameters was not measured in the present thesis. In a study by Maltais et al. [39] greater leg blood flow and oxygen uptake in hyperoxia compared to normoxia was demonstrated in 14 COPD patients, however these results were calculated and not directly measured.

We might speculate that the oxygen availability and thus oxygen pressure was increased in the mitochondria in the patients of the present studies. If so, the patients in study II were exercise limited by the muscles to utilize the increased available oxygen in acute hyperoxia, demonstrated by no further increase in VO_{2peak} compared to normoxia pre or post training.

This suggest a limitation in the peripheral working muscles to consume the available oxygen with no reserve capacity during whole body work both before and after the training period, indicating an excess of mitochondrial capacity [192]. As two legs VO_{2peak} increased less than one leg VO_{2peak} from pre to post training in study I, it was concluded that the patients had a peripheral muscle reserve capacity when concerning whole body VO_{2peak} after the training period when the peripheral muscles had gained training adaptations exceeding the central limitations to supply the working muscles with oxygen. The difference between whole body VO_{2peak} and one leg VO_{2peak} was reduced after the training supporting the assumption that the peripheral training adaption far exceeds the cardiovascular adaptations. The speculations from study I was partly supported by the findings from study II as it was demonstrated that whole body VO_{2peak} increased less than one leg cycling indicating a reserve capacity in the peripheral muscles during two legs cycling. However, the assumption that the main limitation was oxygen availability became weakened as acute hyperoxia with concomitant increased arterial oxygen saturation did not increase VO_{2peak} compared to normoxia. This demonstrates that the reduced peak whole body capacity compared to one leg work might not have been an oxygen saturation limitation. It might rather be a ventilation and/or oxygen delivery limitation through decreased blood flow or diffusion limitation, resulting in the peripheral skeletal muscle reserve capacity during whole body performance. In study III, acute administration of hyperoxia resulted in increased VO_{2peak} compared to normoxia both before and after the training intervention in the normoxic peak exercise hypoxemic COPD patients, indicating a supply limitation to deliver oxygen to the periphery by the cardiopulmonary system during normoxic conditions. This is supported by the findings that hyperoxia improves muscle electrical activity during dynamic exercise and that the hypoxemia-induced skeletal muscle dysfunction most probably acts through mechanisms based on oxygen availability [191]. The findings concerning the difference in normoxic and hyperoxic response on VO_{2peak} between study II and III might be due to the great difference in arterial oxygen saturation in study III between normoxia and hyperoxia, which were 13% higher in hyperoxia at pre and post test. Severe COPD patients with hypoxemia at peak exercise thereby seems to have the same exercise limitations as highly trained endurance athletes as it is stated that exercise training appears to result in a switch from metabolic demand limitation to oxygen supply limitation of peak exercise [31].

5.3 Work economy

Submaximal VO_2 at a standard work load was reduced by 10% after 8 weeks of aerobic high intensity interval treadmill walking in the COPD and CAD patients (III). Thereby the patients were able to perform 5 minutes of treadmill walking at 20 and 40 watts respectively with a significantly lower oxygen demand post training compared to pre training. Increased strength and VO_{2peak} in COPD might slow the reliance upon type II muscle fibres as exercise intensity increases and lead to an improved muscular work [49, 112]. To be able to perform daily activities and maintain a satisfactory quality of life, an improved work economy might be crucial in COPD patients as their exercise capacity is extremely poor [1]. Maximal strength training improves mechanical efficiency, rate of force development and pulmonary function in COPD patients by 32, 105 and 22% respectively, pre to post 8 weeks of training [100]. This might be translated into either having the potential to perform significantly more work, or to perform the same work with a reduced effort without an increased VO_{2peak}. A training intervention consisting of both aerobic high intensity interval training and maximal strength training would thus be beneficial for further improvement in work economy.

5.4 Quality of life

An improved measure outcome of the SF-36 health related quality of life questionnaire was detected after 8 weeks of aerobic high intensity interval treadmill walking in the COPD patients (III). Both physical and psychical states had improved pre to post training by 24 and 35% respectively. The patients improved VO_{2peak} and work economy pre to post training by 19 and 10% respectively. These improvements most likely had influenced daily living to a great extent resulting in an improved self percepted quality of life questionnaire outcome. As the modality of training was walking, the great improvements in quality of life score can be explained by the fact that walking is the kind of exercise mostly involved in the patient's usual activities, and the improved exercise capacity is thereby well experienced throughout the subject's daily routine. Increased quality of life has also been demonstrated by others after strength and endurance training interventions [100, 126, 202, 224] and is an important aspect when including endurance training into clinical practice for COPD patients.

5.5 Limitations

A challenge during the work of the present thesis was to recruit COPD patients willing to participate in a training intervention. A low number of participants might be looked upon as a

weakness of the studies as minor differences might not be significant. However, even with a small number of subjects in the groups, significant differences was demonstrated and thereby strengthens the results. A longer training period than in the present studies might also have increased VO_{2peak} to a even greater extent than what was found after eight weeks.

5.6 Perspectives

COPD is one of the most rapid increasing diseases that world-wide is afflicting millions of people. It is important to reveal strategies to prevent morbidity and mortality in these patients in an effective manner both to improve quality of life for the patients and due to the economic burdens of the society. As the disease itself is not fully reversible, rehabilitation has to focus on how to gain optimal physiological adaptations and mobility in spite of the disease. In theory, exercise is well accepted as a part of any rehabilitation program, however until now there has not been a clear recommendation of training modality. There is a strong correlation between endurance capacity expressed as VO_{2max} and the risk for mortality, morbidity and immobility. Whereas most COPD patients demonstrates low VO_{2peak} that declines over time, exercise strategies which emphasise effective improvement in VO_{2peak} should be in focus.

The present studies demonstrates that intensity is the most important factor to improve VO_{2peak} in COPD patients. An overall conclusion is that due to the pulmonary disease, interventions that maximally challenge working muscle oxidation and taxes ventilation to a lesser degree, is the main factor in improving VO_{2peak}. Training with a reduced muscle mass was found to be effective in severe COPD patients as ventilation was relatively reduced and thereby the muscular work increased. In severe COPD patients with hypoxemia during exercise, hyperoxia increases arterial oxygen saturation and allows for a greater training intensity at the same ventilatory load. The findings from the present thesis adds important information on improvements in exercise capacity in COPD patients. One leg training, as well as hyperoxia for patients with hypoxemia during exercise, should be implemented as a main strategy in future clinical practice. Understanding and communicating new developments in physiological research is the least of the problems in terms of changing existing rehabilitation practises. The challenge is to ensure that this information is acted upon by medical doctors and patients.

6 Conclusions

Aerobic high intensity interval one and two legs cycling at 85-95% of peak heart rate significantly increased whole body VO_{2peak} and work load pre to post training. A significantly greater increase after one leg cycling compared to two legs cycling was found. The work load performed leg by leg is greater than when working together, however the ventilatory load is not different. Thereby the relative ventilation is reduced during the one leg cycling which allows the patients to train at a higher muscle-specific intensity compared to whole body exercise resulting in a significantly greater training response. These results indicate a demand rather than a central limitation to VO_{2peak} in these COPD patients.

Aerobic high intensity one leg interval cycling at 85-95% of peak heart rate in hyperoxia and normoxia significantly increased VO_{2peak} and work load in both one and two legs cycling with no additional training effect in hyperoxia compared to normoxia. Increased arterial oxygen saturation per se. in acute hyperoxia at pre and post test failed to increase VO_{2peak} above the level attained in normoxia even though peak work load were significantly higher, indicating a demand limitation to consume oxygen in the peripheral muscles.

Hyperoxic aerobic high intensity interval training at 85-95% of peak heart rate in COPD patients with hypoxemia at peak exercise improved VO_{2peak}, peak work load, work economy and quality of life pre to post training. Acute hyperoxia increased VO_{2peak} and peak work load significantly more at pre and post test compared to normoxia in the COPD patients. This indicates an oxygen supply limitation to VO_{2peak} in normoxia, whereas no difference between acute hyperoxia and normoxia suggesting oxygen demand limitation in the CAD patients.

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1978

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1979

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1980

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