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Training is Medicine; Endurance and Strength Training in Coronary Artery Disease and Health

Thesis for the degree philosophiae doctor

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Norwegian University of Science and Technology
Faculty of Medicine
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NTNU

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Trening er medisin:

Optimal utholdenhets og styrketrening hos koronar pasienter og friske mennesker

Intervalltrening med høy aerob intensitet ved 90-95% av maksimal hjerte frekvens er mer effektiv enn kontinuerlig trening med lav til moderat intensitet for å forbedre maksimalt oksygenopptak blant friske unge menn. Maksimalt hjerteminuttvolum økte i samme omfang som maksimalt oksygenopptak, men bare i gruppene som trente høy aerob intensitets intervall trening. Høy aerob intensitets utholdenhetstrening er signifikant mer effektivt enn trening på laktatterskel (85% av maksimal hjertefrekvens) og på 70% av maksimal hjertefrekvens, for å øke maksimalt oksygenopptak og hjertets slagvolum. Økningen i maksimalt oksygenopptak korresponderer med forandringer i slagvolum, og indikerer at det eksisterer en nær sammenheng mellom disse to parametrene.

Høy aerob intensitets intervall trening på 85-95% av peak hjerte frekvens gir en signifikant økning i hjertets slagvolum samt venstre ventrikkels ejeksjonsfraksjon i pasienter med koronar hjertesykdom. Høy aerob intensitets intervall trening øker hjertets peak slagvolum og venstre ventrikkels ejeksjonsfraksjon som en funksjon av økt myokard kontraktilitet og bedring i venstre ventrikkels systoliske funksjon.

Intervall trening i hyperoksi (100% oksygen) gav ingen effekt utover intervall trening i normoksi (21% oksygen) hos pasienter med koronar hjertesykdom med mild til moderat iskemi. Trening i hyperoksi økte VO_{2peak} og peak slagvolum tilsvarende som trening i normoksi. Ettersom akutt eksponering til hyperoksi ikke forbedret VO_{2peak} konkluderes det med at koronarpasienter har en perifer oksygen begrensning for VO_{2peak} i forkant og i etterkant av 10 uker med trening i hyperoksi.

Trening av maksimal legg press med fokus på få repetisjoner med tung belastning og maksimal konsentrisk kontraksjon øker maksimal muskel styrke, kraftutviklingshastighet, og mekanisk gang effektivitet hos koronarpasienter gjennom et minimum av trening. Økning i muskelstyrke og kraftutviklingshastighet kan overføres til bedret mekanisk effektivitet under gang, tilsvarende friske menn i samme aldersgruppe.

Bakgrunnen for å gjennomføre studiene var et ønske om å undersøke effekten av utholdenhetstrening med ulik intensitet og varighet, men med identisk energiforbruk. I tillegg ønsket vi å undersøke nye aspekter og mekanismer knyttet til intervalltrening med høy aerob intensitet blant hjertepasienter, samt å undersøke effekten av maksimal styrketrening på muskestyrke, reaksjonshastighet og submaksimal utholdenhet i denne pasientgruppen. Studiene i denne avhandlingen er gjennomført som kontrollerte treningsintervensjoner, men testing av blant annet utholdenhet, muskelstyrke og hjertefunksjon i forkant og etterkant av en 8-10 ukers treningsperiode.

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Content

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Trine Karlsen

Preface

The following thesis is based upon an introduction to the field, a summary of the thesis, and the papers listed below. The work for this degree was carried out in the laboratory for exercise physiology and sports science at the Department of Circulation and Medical Imaging, The Faculty of Medicine, The Norwegian University of Science and Technology and the Department of Cardiology, University Hospital of Aarhus, an is to be concluded with the degree PhD in clinical medical research.

Paper I

Jan Helgerud, Kjetil Høydal, Eivind Wang, Trine Karlsen, Pål R Berg, Marius Bjerkaas, Thomas Simonsen, Cecilie S Helgesen, Nina L Hjorth, Ragnhild Bach, Jan Hoff: Aerobic High-Intensity Intervals Improve VO_{2max} more than moderate training. Medicine in Science in Sports and Exercise 2007; 39: 665 – 671.

Paper II

Jan Helgerud, Trine Karlsen, W Yong Kim, Kjetil L Høydal, Asbjørn Støylen, Henrik Pedersen, Lau Brix, Steffen Ringgaard, Jørn Kværnes, Jan Hoff: How to Improve Stroke Volume in Heart Patients

Paper III

Trine Karlsen, Jan Hoff, Asbjørn Støylen MD, Mie Cappelen Skovholdt, Kari Guldbrandsen Aarhus, Jan Helgerud: Aerobic interval training improve VO_{2peak} in heart patients; no additional effect from hyperoxia. Scandinavian Cardiovascular Journal. In Press

Paper IV

Trine Karlsen, Jan Helgerud, Asbjørn Støylen, Nina Lauritsen, Jan Hoff: Strength Training Restores Walking in Heart Patients.

Definitions

Maximal oxygen uptake (VO_{2max}): The highest oxygen uptake achieved during dynamic exercise with large muscle groups. VO_{2max} is by most authors regarded as the best single measure of aerobic endurance.

Peak oxygen uptake (VO_{2peak}): The highest oxygen uptake achieved in a patient population where all the criteria for VO_{2max} cannot be fulfilled.

Mechanical work efficiency: The efficiency of skeletal muscles to transform biomechanical energy into the external work of movement.

Work Economy: The ratio between oxygen cost and exercise load.

Lactate threshold: The level of exercise where equilibrium between production and removal of lactate exists.

Cardiac output (CO): The volume of blood ejected into the main artery by each ventricle. Normally cardiac output is expressed as litres per minute. Both ventricles eject the same amount of blood with only small fluctuations.

Stroke Volume (SV): The volume of blood ejected from the ventricle into the main artery each heart beat. Normally stroke volume is calculated through dividing the cardiac output by the heart rate.

Ejection fraction (EF): The percentage of the end diastolic volume ejected as stroke volume.

Maximal muscular strength: A muscles maximal potential to develop force.

Rate of force development: The ability to produce force per time unit.

Hyperoxia: Inspiration of a gas mixture with an oxygen content exceeding ambient air.

Abbreviations

VO_{2max}	Maximal oxygen uptake
VO_{2peak}	Peak oxygen uptake
a-vO_2 difference	Arterio-venous oxygen difference
1RM	One repetition maximum
PO_2	Partial pressure of oxygen

Summary

High aerobic intensity interval training at 90-95% of maximal heart rate is more effective than continuous training with low to moderate intensity in improving maximal oxygen uptake in healthy young men. Maximal cardiac stroke volume was improved to a similar extent in high aerobic intensity interval training only. It is concluded that high aerobic intensity endurance training is significantly more effective than isocaloric training at lactate threshold (85% of maximal heart rate) or 70% of maximal heart rate, in improving maximal oxygen uptake and cardiac stroke volume. Improvements in maximal oxygen uptake corresponded with changes in stroke volume, indicating a close link between the two.

High aerobic intensity interval training at 85-95% of peak heart rate significantly improves peak cardiac stroke volume and resting left ventricular ejection fraction in coronary artery disease patients. High aerobic intensity interval training improves peak cardiac stroke volume and left ventricular ejection fraction in coronary artery disease patients due to increased myocardial contractility and enhanced left ventricular systolic performance.

Hyperoxic high aerobic intensity interval training at 85-95% of peak heart rate gave no additional effect over normoxic high aerobic intensity interval training in coronary artery disease patients. Hyperoxic training improves VO_{2peak} and peak stroke volume to the same extent as ambient air training in stable coronary artery disease patients with mild to moderate coronary ischemia. As acute hyperoxia did not increase VO_{2peak} it is concluded that the coronary artery disease patients showed peripheral oxygen limitations in VO_{2peak} both before and after 10 weeks of hyperoxic training. Hyperoxic training may thereby represent no increase in cardiovascular shear stress.

Maximal leg press exercise focusing on few repetitions with heavy loads and maximal concentric contractions improves maximal strength, rate of force developments and walking mechanical efficiency in coronary artery disease patients through a minimal exercise effort. Improved muscular strength and rate of force development translates into improved walking mechanical efficiency returning the patients work efficiency to the levels of healthy age matched subjects.

1 Introduction

Maximal oxygen uptake (VO_{2max}) has been named the prognostic variable that does not get enough attention in cardiac medicine. This in spite of the history of epidemiology research documenting the importance of physical training as a protecting agent for the development of cardiovascular disease, ranging from the early Greek philosophers to the modern epidemiology work introduced by professor Jeremy N. Morris in the 1950's [101, 127].

Cardiovascular disease includes the diagnosis hypertension, ischemic heart disease, stroke, arrhythmia, congestive heart disease and valvular disease. The most common form of heart disease is coronary heart disease most often caused by atheroma and complications following thereafter, and thrombosis in particular [197]. Coronary artery stenosis impair myocardial blood flow leading to ischemia, reduced myocardial contractile function and may eventually result in myocardial infarction and death [161]. The cardinal symptoms of coronary heart disease are dyspnoea, chest pain or discomfort, cyanosis, syncope, palpitation and edema, together with dyspnoea and fatigue at low effort [135, 197].

Cardiovascular disease is the dominant chronic disease accounting for ~50% of all deaths in developed countries [197]. Coronary heart disease is the leading cause of death, and a major cause of physical disability in the United States [2]. By the year 2020 cardiovascular disease is predicted to be the number one cause of death and disability accounting for one in every three deaths, claiming 25 million lives annually. Cardiovascular disease requires expensive treatment, pharmaceuticals alone costing $36 billion in the United States in 2001, counting for 19% of all drug costs [197]. Despite major advances in pharmacological treatment a number of heart failure patients suffer from dyspnoea, fatigue, reduced exercise capacity and poor quality of life [177], and a higher prevalence of disability is reported compared with healthy age matched individuals [138].

1.1 Aerobic endurance

Aerobic endurance is defined as the ability to perform large-muscle, whole body exercise at moderate to high intensities for extended periods of time [129]. Aerobic endurance depends on the supply of oxygen and nutrients to the working muscles, the muscles ability to metabolise nutrients and the removal of metabolites produced [199]. VO_{2max}, anaerobic threshold and work economy or efficiency (i.e. the oxygen cost to generate a given work load)

has been identified as the primary influencing factors to aerobic endurance performance [87, 129].

1.2 Maximal oxygen uptake

Maximal oxygen uptake is in most publications regarded the single best predictor of aerobic endurance [96], defined as the highest oxygen uptake an individual may attain during exercise engaging large muscle groups while breathing air at sea level [129, 200]. VO_{2max} is largely determined by maximal cardiac output, the oxygen carrying capacity of the blood and the oxidative capacity of the active skeletal muscle tissue [87, 129]. VO_{2max} can be displayed as $VO_{2max} = (HR \cdot SV) \cdot a\text{-}vO_2$ difference ,where heart rate (HR) times stroke volume (SV) equals cardiac output (QO) and the arterio-venous oxygen difference (a-vO_2 difference) is the difference in oxygen content in arterial and venous blood [12]. Oxygen uptake increases linearly with increasing power output [182]. For each litre of oxygen consumed, about 5 kilocalories of energy output will be delivered, thereby a greater oxygen uptake results in a larger aerobic energy output [199]. VO_{2max} is a good predictor of endurance sport performance [156], and are exercise specific with 10 - 20% lower VO_{2max} observed in stationary biking compared to treadmill exercise [111]. Variability in VO_{2max} are observed due to body size, muscle mass, genetics, age, gender and conditioning status [87, 129]. The term peak oxygen uptake (VO_{2peak}) is more commonly used to express exercise capacity in patients with cardiovascular and pulmonary disease due to inability to achieve the VO_{2max} criteria [12].

1.3 VO_{2max} , aging and inactivity

VO_{2max} is dictated by the health and efforts of the pulmonary, cardiovascular and skeletal muscle system, and reflects the ability to perform day to day activities [12]. The cardiovascular systems functional capacity declines with aging [151, 166, 173, 191, 200] and inactivity [105], on average 10% per decade in healthy adults [173]. It is debated whether reduced VO_{2max} is due to aging itself or a decrease in activity level [191]. Lifelong endurance training forestalls the age related reduction in VO_{2max} [89, 152], resulting in higher VO_{2max} than in inactive age matched individuals, and values comparable to untrained young men [25]. VO_{2max} may be reduced with age in physically active men as well, but remains higher at all ages compared to inactive individuals [191]. 3 weeks of complete inactivity dramatically reduce VO_{2max} to the same level as 30 years of aging [105]. The age-related decline in VO_{2max} may be caused by the maximal cardiac output or the a-vO_2 difference, with maximal oxygen delivery most likely the major contributor to the age-related decline in VO_{2max} [173].

1.4 Cardiopulmonary exercise testing

Cardiopulmonary exercise testing may bring forth cardiovascular abnormalities not present at rest. Together with electrocardiography it is the most frequent non-invasive diagnostics of coronary artery disease [197], and a good predictor of health status and prognosis [136]. Exercise testing is considered safe in most cardiovascular disease populations with a mortality and morbidity of less than 0.01 and 0.05 percent respectively [197].

1.5 Safety of testing and training

Vigorous physical activity acutely increases the risk of myocardial infarction and sudden cardiac death in susceptible individuals. Exercise related cardiac events may occur in individuals with structural cardiac disease. The risk is greatest after an acute ischemic event [197], and atherosclerotic disease is often the main triggering factor [176]. The incidence of myocardial infarction and sudden death is greatest in the habitually least physically active individuals and in subjects with low physical fitness [23, 47, 114, 128, 144, 176], while regular physical activity reduce the incidence of cardiovascular events [114, 128] and mortality [23, 114, 128]. High MET levels (1MET = 3.5 $ml \cdot kg^{-1} \cdot min^{-1}$) is inversely associated with prevalence of carotid atherosclerosis in hypertensive men [85], and the incidence of cardiac arrest decrease with increasing level of habitual activity [163]. Improvements in risk factors associated with coronary artery disease may prove important for death risk and the development of cardiovascular disease [175]. Thereby it is essential not to overestimate the risk of training since the benefits outweigh the risk [176]. Heart failure patients may safely take part in exercise training and thereby reduce mortality risk and hospital admission rate [137].

1.6 Mortality

VO_{2max} is an important predictor for cardiovascular and all cause mortality and morbidity. High VO_{2max} corresponds with lower death rates in all age groups [57, 113, 117], and are together with exercise energy expenditure an important predictor of all-cause and cardiovascular mortality [116]. An improvement in VO_{2max} by 1 MET (3.5 $ml \cdot kg^{-1} \cdot min^{-1}$) may improve the risk of mortality by as much as 12-17% [57, 117]. Training significantly reduce clinical events [106], mortality and hospital admission rates in heart failure patients [4, 137]. Patients enrolled in cardiovascular exercise programs reduces cardiovascular deaths by 20-25% whereas the occurrence of cardiac events is more frequent in patients not training [19].

1.7 Cost of treatment

Training after coronary artery disease events is economically favourable, reducing the costs associated with rehospitalization [4, 42]. Aerobic endurance training has shown superior cost effects compared with standard treatment. The combination of training and life style changes compared with percutaneous transluminal coronary angioplasty treatment proved to be twice as cost effective, with less cardiac events and the intervention demonstrating improvements in aerobic power [65]. Training has a positive economically potential in rehabilitation after cardiac events, as it is safe, effective and relatively pleasant treatment with moderate costs compared with alternative therapy [4]. The mortality and cost aspects highlights the importance of employing effective endurance training in treatment and prevention of cardiovascular disease [101], and the large direct and indirect costs of coronary artery disease does call for a justification of the economy of medical benefits (42).

1.8 Endurance training

Training entails exposing the organism to a training load or work stress of sufficient intensity, duration and frequency to produce structural and functional adaptations resulting in a noticeable measurable training effect in the function one is training [102, 199]. Endurance events are activities lasting for 2 minutes or more [29]. Endurance training is an effective means for improving VO_{2max}, and the most striking adaptations include increased cardiac stroke volume and capillary- and mitochondrial density [87, 102]. Improvements in VO_{2max} are related to training intensity, duration and frequency [141]. The minimum intensity for initiation improvements in VO_{2max} seems to be 55-65% of maximal heart rate [200], whereas elevated training responses are observed with high intensity training [186]. Comparison of training protocols matched for total work and frequency, report high aerobic intensity interval training between 85 to 95% of maximal heart rate, to be more beneficial for improving aerobic power than continuous training at lower intensities in both healthy individuals [174] and cardiovascular disease patients [153, 193]. Other investigators does not detect a difference between continuous and interval training when the training was performed at the same intensity [126].

1.9 Endurance training in coronary artery disease patients

Reduced VO_{2peak} is reported in heart failure patients. Similar skeletal muscle impairments as with physical deconditioning are observed and may influence VO_{2peak} more than myocardial abnormalities [108]. The magnitude of reduction in VO_{2max} and coronary function may also depend on the level of ischemia and/or the size of prior myocardial infarction [8]. Substantial

epidemiological, clinical and basic science suggest that physical activity and training delays the development of atherosclerosis, reduces the incidence of coronary heart disease events [176], and reverses skeletal muscle abnormities [108]. The American heart association supports the use of training as a means to optimize cardiovascular risk reduction and promotes an active lifestyle for cardiovascular disease patients [14, 175]. Training in cardiac rehabilitation serves as a valuable non-pharmacologic intervention improving VO_{2peak} and overall health status in patients with coronary artery disease [184].

Heart failure patients significantly improves VO_{2peak} as a result of endurance training [153, 164, 177, 193]. Training intensity is critical for maintaining VO_{2peak}, endurance and cardiac enlargement [71]. High intensity training is twice as effective in increasing VO_{2max} as conventional cardiac rehabilitation programs [58], successfully improving VO_{2peak} and health status in coronary artery disease patients [184]. High aerobic intensity interval training is superior to isocaloric moderate intensity training in improving VO_{2peak} in cardiovascular disease patients [153, 193]. Neither interval training nor traditional aerobic programs increases the risk to the patients [184], and high intensity training maintains or improves cardiovascular function and the risk of further atherogenesis [58]. Endurance training elevates the angina threshold partly through reduced submaximal heart rate, and the long term effect of training may be equal to the short term effects of nitro-glycerine use [36].

Aerobic endurance training initiates several cardiovascular and health benefits in addition to increasing VO_{2peak}. Reductions in blood pressure, low density lipoprotein, total cholesterol level and body weight are reported [58, 115, 124] together with increase in high density lipoprotein levels, and improved endothelial function, blood glucose and insulin sensitivity [58]. Resting bradycardia is reported improved, peripheral venous tone increased, and plasma volume expands improving central blood volume and ventricular preload. Also myocardial contractility and stroke volume improves [162, 177, 193], together with a net reduction in thrombogenic risk and improved blood rheology [35, 53].

Despite numerous reports and recommendations from expert panels on the importance of training in prevention of cardiovascular disease less than one third of Americans meet the minimal recommendations outlined by the centre for disease control and prevention, the American College of Sports Medicine and the American Heart Association [115], implying that the implementation of endurance training in the coronary artery disease population is

challenging. Only 10-20% of eligible patients participates in cardiac rehabilitation programs [2], and trials struggles with low long-term compliance with non medical dropout reasons [4]. Comparison of supervised and home based training programs found 3 months of supervised training to be as effective as 12 months of home based training implying that some level of supervision is required for successful training management [109]. Individual programs with close follow up are therefore recommended as rehabilitation and secondary prevention for coronary heart disease patients [2].

1.10 Stroke Volume

Stroke volume does not seem to plateau from rest to maximal exercise in endurance trained athletes, in contradiction to earlier believes [50, 54, 196]. A plateau exists at different submaximal levels in untrained subjects and university athletes [54, 196], with a secondary increase in stroke volume at heavy work loads in some cases [50]. The large stroke volumes recorded in endurance athletes is a results of enhanced cardiac chamber and pericardial compliance producing a greater end-diastolic volume or a larger left ventricle dimension [96, 192]. The diastolic filling and left ventricle emptying rate is significantly faster in endurance trained athletes compared with moderately trained subjects [50]. At a heart rate of 190 beats $\cdot$ min^{-1} ventricular emptying and filling rate were 20% and 71% greater in elite athletes versus untrained subjects, making ventricular filling the athletes' major advantage implying a considerably enhancement in ventricular preload and/or compliance [50, 54].

The majority of evidence supports that maximal cardiac output decrease with aging through reduced maximal stroke volume and reduced maximal heart rate [173], and that a sedentary lifestyle in addition deteriorates coronary function with left ventricular stiffness, decreased left ventricular compliance and diastolic performance [11, 151]. Endurance trained individuals displays greater stroke volume, ventricular filling, systolic and diastolic left ventricular function and cardiac contractility compared with active and sedentary subjects [24, 25].

In coronary artery disease patients endurance training increases peak stroke volume and improve left ventricular function [43, 44, 58, 63]. Training reducing myocardial ischemia may increase left ventricle contractile function [43, 58]. Improved stroke volume and left ventricle ejection fraction is associated with reduced peripheral resistance and cardiomegaly [46, 63]. Endurance training reverse myocardial remodelling through reduced left ventricle end

diastolic diameter [20, 63]. Intensity dependency has been reported in the myocardial response to endurance training. High intensity endurance training has a greater effect on rest to peak left ventricular ejection fraction [123] and on reversing myocardial remodelling than moderate training [193]. Training and detraining in older men gives qualitatively and quantitatively similar changes in left ventricular performance, however directionally opposite, abolishing the diversity in cardiovascular performance, and highlights the importance of endurance training for maintaining myocardial function and capacity [160]. Preserved ventricular compliance in endurance training elderly may possibly prevent heart failure [11].

1.11 Myocardial perfusion

Endurance training may reverse the cardiovascular disease through a regression of stenosis, reducing the number of angina episodes [124] and decelerate the development of coronary artery disease [121]. Endurance training improves coronary perfusion and reduces ischemia in all ischemic areas while percutaneous transluminal coronary angioplasty treatment only improved perfusion in the treated stenosis area [90]. Increased coronary perfusion after endurance training in cardiovascular disease patients indicates increased microcirculation in the ischemic segments of the myocardium [194]. This may be a result of improved endothelial function and vasoregulation through elevated nitric oxide syntheses expression [61, 66] and regression in coronary atherosclerosis [67]. Improvements in coronary collateralization [37, 159] and increased myocardial capillary density [187] have been observed in animal training models, but are still controversial in humans [20, 121]. Some authors report no difference in collateral formation with training [121], while other reports collateral formation with training [20].

1.12 Endothelial function

The endothelium maintains vascular homeostasis through interactions between cells in the vessel wall and lumen. This includes regulation of vascular tone through nitric oxide and other vasoconstrictors, platelet inactivity, and production of cytokines and adhesion molecules active in inflammation [98, 188]. Endurance training improve endothelium mediated vasodilatation in peripheral vasculature [62, 99], and myocardial arteries in patients with atherosclerosis [61, 66]. This reverses the peripheral vascular resistance caused by endothelial dysfunction [195].

1.13 Limitations to exercise

A classic question in human physiology is which link in the body's oxygen transport system that limits VO_{2max} [155]. Some authors claim that the integrated effect of all steps in the respiratory cascade helps set the VO_{2max}, since a change in any step will alter VO_{2max} [76]. Current knowledge does however separate between limitations in the supply of oxygen or demand limitation in the peripheral skeletal muscles [12]. Muscle blood flow is closely related to the oxygen demand of the exercising muscles, and a large increase in muscle perfusion and oxygen delivery is observed during small muscle mass exercises, indicating that the vascular bed in skeletal muscles does not limit oxygen transport [9]. Redistribution of blood and capillary mean transit time is crucial for oxygen extraction and the a-vO_2 difference. During whole body exercise the cardiac output is not sufficiency large to allow for the same level of muscle capillary blood supply as observed during smaller muscle exercise [155]. Factors limiting VO_{2max} has been thoroughly investigated with data supporting the notion that oxygen supply limits VO_{2max} in the healthy human skeletal muscles [92, 147-149, 157, 181]. A separation between supply limitation in VO_{2max} in athletic individuals and metabolic limitations in VO_{2max} in unfit subjects, with exercise training serving as a switch in the relationship from metabolic towards supply limitation has been suggested [182]. Patients with severe chronic heart failure develop depressed oxidative capacity in the skeletal muscles decreasing VO_{2peak}. This implies that the functional capacity of heart failure patients is not merely limited by oxygen supply, but by the oxidative capacity of mitochondria in working muscle as well [41].

1.14 Hyperoxia, performance and exercise

Hyperoxia is defined as inspiration of oxygen at pressures greater than air at sea level, with no more than 1 atmosphere absolute pressure [185]. The oxygen supply to the skeletal muscle is a function of the arterial oxygen content and muscle blood flow [56]. Breathing hyperoxic gas increases the arterial and tissue partial pressure of oxygen (PO_2) and the haemoglobin oxygen saturation, providing additional oxygen supply to the working skeletal muscles.

Acute exposure to hyperoxia increases VO_{2max} and performance in endurance athletes [130-132, 145, 148], and in healthy- and untrained subjects [33, 45, 92, 139], and allows for training at a greater intensity compared to normoxia [134, 140]. In the trained skeletal muscle hyperoxia elevate intracellular PO_2 and VO_{2max}. The increase in VO_{2max} is however disproportional to PO_2 suggesting that the trained skeletal muscle at times may be at

borderline in terms of supply limitations [149]. A coronary ischemic limitation to exercise is defined as the angina threshold. Hyperoxia may elevate the angina threshold in heart patients, allowing the heart to perform more work before the development of coronary insufficiency [77], increasing the exercise performance [1, 77, 112, 142, 150]. Some authors recommend the use of hyperoxia during training to patients with angina pain [142]. Others observe no improvements in performance and leg oxygen consumption in heart failure patients exposed to hyperoxia [146, 154], probably implying some variations within the patient population. Two training studies have investigated the effect of hyperoxic training in healthy subjects, demonstration significantly increased training load, without any significant effect on VO_{2max} after 5- and 6 weeks of training [134, 140].

1.15 Skeletal Muscular Strength

Skeletal muscle strength is defined as the integrated result of several force-producing muscles performing maximal isometric or dynamic contractions during a single voluntary effort in a defined task [73]. Maximal strength is defined as one repetition maximum (1RM) in a standardized movement [72], and power is a product of force inversely related to time [73]. The ability to create as much force as possible in the shortest possible time is named rate of force development. A skeletal muscle's ability to develop force depends on several factors including initial position, speed of muscular- lengthening and shortening, eccentric initial phase, type of muscle fibres, muscle cross- sectional area, number of motor units activated simultaneously, impulse frequency, and substrate availability [102].

Muscular strength decreases with age and inactivity [21, 95, 143, 179], and is associated with diminished functional capacity of the neuromuscular, neuroendocrine, cardiovascular and respiratory systems [83]. Reduced skeletal muscle strength is associated with reduced muscle mass through loss of skeletal muscle fibres secondary to decreased number of motoneurons, gradually aggravating health and physical function [40, 119, 143]. Reduced skeletal muscle strength in coronary artery disease patients may be due to long term bed rest and inactivity arising from the fear of the consequences of training. Inactivity leads to deconditioning and progressively reduced skeletal muscle strength and volume [120]. Skeletal muscle atrophy has been observed in heart failure patients [100], and the prevalence of sarcopenia may be as high as 30% in the above 60 year old population [40]. Sarcopenia and reduced neuromuscular function may explain lower maximal skeletal muscle strength in heart patients compared with healthy subjects [30, 100]. In coronary artery disease patients reduced physical capacity are in

many cases the result of reduced skeletal muscle function, and can be unrelated to cardiovascular function [109]. Aging and inactivity leads to reduced muscle mass and increased prevalence of disability. With reduced skeletal muscular strength follows a progressive loss of function and capability of day to day activities, and loss of independence [40]. Quality of life is affected negatively by diminished muscular strength and endurance, as is the ability to complete physical tasks [80]. Middle age and older coronary artery disease patients state a greater levels of physical disability in daily life compared with healthy age matched individuals [138].

Reduced skeletal muscle strength may also be due to reduced neuromuscular response and voluntary neural drive to the muscle [82, 84, 97], or high antagonist muscle activity limiting movement efficiency [84]. Reduced rate of force development has been demonstrated in healthy elderly compared with younger individuals [84, 179]. Elderly individuals with a high level of disuse have a marked loss of muscle mass and strength. Reduced neuromuscular activation, contractile function and rate of force development are more affected by disuse than maximal muscle strength [170]. Coronary artery disease populations have a high prevalence of obesity, with body mass indexes exceeding 25, in 50 to 88% of the patients [13, 27]. Strength training has the capability of altering the body composition from fat to muscle tissue [80]. Elevated body fat is associated with reduced walking speed, and functional limitations in daily life, while increased levels of muscle mass is associated with faster walking speed and less limitation to daily functionality [167]. In a cardiac rehabilitation setting weight loss is effective in reducing body fat and total cholesterol and scores for physical function [158].

1.16 Strength training

Skeletal muscular strength enhancement is made possible through muscular hypertrophy and/or neural adaptation. With hypertrophy the muscle fibre myofibril content increase in association with elevated muscular strength and body weight [55]. Strength training reverse sarcopedia [143, 178], inflicting hypertrophy and increase skeletal muscular strength [52]. Muscle atrophy is distinctive for chronic heart failure patients [180], and muscular strength is a strong predictor of survival in severe congestive heart failure patients [79]. With progressing New York Heart Association grading, muscle metabolism is aggravated, and skeletal muscle function seems to be one of the crucial end points in the evaluation of physical conditioning [10, 79, 189]. Resistance training has the potential of treating myopathy and muscle weakness occurring in the majority of heart failure patients [180]. Disabled older female coronary heart

disease patients performing resistance training increased both physical activity and total energy expenditure [5], together with improved muscular strength, physical capacity in household activities, endurance, balance, coordination and flexibility, making resistance training an important rehabilitation component [6]. Strength training has in some cases been found to improves test scores for physical function [28], and lower risk factors associated with coronary artery disease [15, 81] most likely through increased activity levels.

Muscular strength improvement strategies without weight gain may be advantageous in the coronary artery disease population since transportation of a greater body mass is undesirable. Strength training to impose neural adaptations includes recruiting the fastest motor units through training with a rapid movement action. In practical terms it means that dynamic movements, few repetitions (three to five), heavy resistance (85-100% of 1RM) and explosive movements are implied [18, 93]. Maximal strength training emphasizing neural adaptations [17] is an effective means for improving 1RM and rate of force development in healthy subjects [7, 72, 74, 93, 125], and chronic constructive pulmonary disease (COPD) patients [75]. The improvement in skeletal muscular strength and power has been linked to neural adaptations and increased voluntary activation of agonists and reduced antagonist coactivation in elderly subjects [59, 60], leading to better walking actions [59]. Resistance training evoked both the V-Wave and the H-reflex responses during maximal muscle contraction, increasing the motoneural output that may include central motor drive, elevated motoneuron exitability and reduced presynaptic inhibition [198].

1.17 Muscular strength and endurance performance

Work economy is referred to as the ratio between work output and oxygen cost. At a standard running velocity individual variations in oxygen costs exist [31, 68, 69]. Mechanical work efficiency is defined as the efficiency of skeletal muscles to transform biomechanical energy into the external work of movement [133]. For healthy subjects normal walking efficiency is approximately 25 % [133]. The metabolic cost of walking is increased in healthy older adults [110], and reduced walking mechanical efficiency is found in both COPD and coronary artery disease patients negatively affecting walking performance [78]. The increased level of disability reported in coronary artery disease patients may in part be linked to reduced walking efficiency, diminishing the ability for day to day movements [78]. The association between muscular strength and endurance performance is important, given that in addition to increasing 1RM, strength training of the legs also improves endurance performance [70].

Maximal strength training has been reported to improve work economy during endurance activities in healthy subjects by ~5-30% [72, 74, 75, 125], and mechanical work efficiency in COPD patients by 32% [75]. Ades et al. [3] found increased walking endurance after strength training in healthy elderly individuals, however this is not the case in all training studies [110]. A minimum of muscular strength are required to manage daily activities. The ability to rapid force development in skeletal muscles (i.e., contractile rate of force development) is an important characteristic contributing to performance of daily activities such as stair climbing and walking together with preventing falls [16, 51, 171]. Weight training with heavy loads improves maximal strength, rate of force development and electromyogram amplitude in long term immobilised patients in a post surgery setting. Rate of force development correlates with walking speed, highlighting the importance of training both the neurological and morphological aspects of the muscle [171]. Increasing muscular strength could mean shifting the load of daily activity from heavy, to tolerable and repeatable [103]. If supervised training result in a more active lifestyle it may increase the outcome of the training above the "dose" of exercise prescribed, and may be considerably greater than the effect of directly prescribed pharmacotherapy [137].

1.18 The safety of strength training in coronary artery disease

Strength training in coronary artery disease patients renders the possibility of an acute increase in blood pressure and disturbed ventricular function. Exercise loads between 40% to 60% and above 95% of 1RM are considered safe due to small increases in blood pressure [22], however both 1RM testing and weight training with heavier loads are well tolerated in coronary artery disease patients [103]. Moderate resistance training did not effect the left ventricular function in coronary artery disease patients [88], and strength and endurance exercise maintained left ventricular function and cardiac volume to the same extent [107]. Elderly subjects increasing 1RM through weight training reveal attenuated circulatory response at pre training loads, highlighting the importance of increasing strength for better circulatory management in daily life activities [104]. When evaluating the electrocardiographic evidence of ischemia during weight lifting, no symptoms were found at 40, 60, 80 and 100% of voluntary contraction in coronary artery disease patients, while ST segment depressions was observed during maximal treadmill exercise. The estimated myocardial oxygen supply-to-demand balance appears more favorable with maximal repetition weight lifting than with maximal treadmill exercise [48].

1.19 Blood volume

Elevated blood volume has been reported in endurance trained subjects and physically active elderly [86, 168]. Decreased blood volume is associated with aging, sedentary lifestyle and found in standard medicated chronic heart failure patients [38, 49, 86]. An increase in blood and plasma volume after aerobic exercise training has been found in some studies [118, 183], but not in others [26].

1.20 Quality of life

The effect of exercise training on quality of life has been studied in heart patients with a wide variety in instruments, patient selection and training interventions [177]. Training improves scores for quality of life significantly, in a clinically meaningful manner [177], and the improvement is in parallel to the improvement in VO_{2peak} [19]. Quality of life improve after short term training interventions [177, 193] while longer training interventions also report improvements in the New York Heart Association functional class score as well [46, 63]. Training improving quality of life is also associated with improved self reported disability in heart failure patients [190].

2 Objective

In the present thesis the main focus was to explore new and improved aspects of endurance and strength training for coronary artery disease patients, with the aim of better clinical practise in the future. In addition we sought to investigate the effect of different aerobic training intensities matched for energy expenditure on healthy subjects.

The aims of the studies were to:

1. Compare the effects of aerobic endurance training of different methods and intensities matched for total work and frequency.
2. Determine to what extent high aerobic intensity interval training affects peak stroke volume and myocardial contractility and function in coronary artery disease patients.
3. Further develop high aerobic intensity interval training for coronary artery disease patients focusing on limitations to endurance training through studying the response to hyperoxic high aerobic intensity interval training.
4. Determine how maximal leg press training with maximal mobilisation, few repetitions and high load effects muscular strength, rate of force development and walking mechanical efficiency in coronary artery disease patients.

3 Methodology

3.1 Oxygen uptake

3.1.1 Walking efficiency

Submaximal oxygen uptake was measured at a work load corresponding to 40 watt during treadmill walking (Technogym runrace, Italy) before and after training in study IV. To define the walking speed corresponding to 40 watts on the treadmill we used the following equation:

$$Km \cdot h^{-1} = \frac{40Watt}{\left[m_b \cdot N\right] \cdot \sin\theta} \cdot 3.6$$

Oxygen uptake was determined through 5 minutes of continuous respiratory measurements (V-max spectra, SensorMedics, USA), and the mean oxygen uptake measured during the last minute of walking was used to calculate the net efficiency through the following equation:

$$Net\ \ efficiency = \frac{Watt \cdot 0.01433 \quad (Kcal \cdot \min^{-1})}{Energy\ use - REE \quad (Kcal \cdot \min^{-1})} \cdot 100$$

REE; Resting energy expenditure

Resting energy expenditure was set to 3.5 $ml \cdot kg^{-1} \cdot min^{-1}$. Both oxygen uptake and watts were converted to kilojoules to allow for calculation of percent mechanical efficiency [78].

3.1.2 Running economy

In study I running economy was determined before and after the training intervention with subjects running 4 minutes at the standardised work load 7 $km \cdot h^{-1}$ and 5.3% inclination (Technogym runrace, Italy). Continuous respiratory measurements were performed and the mean oxygen uptake values from the last minute were used to determine running economy (Cortex Biophysik GmbH, Leipzig, Germany).

3.1.3 Maximal/Peak oxygen uptake

VO_{2peak} was determined after the submaximal test in study II-IV by increasing the work load until subjects reached exhaustion. Continuous respiratory measurements was carried out, and the mean of the three highest 10 seconds continuous breath by breath

respiratory measurements determined VO_{2peak} (V-max spectra, SensorMedics, USA). Walking speed was kept constant while the treadmill inclination was increased 1-3% every minute until VO_{2peak} was reached. The criteria for VO_{2peak} were an R value above 1.0 and a Borg scale value above 15. Heart rate was recorded (Polar sports tester, Finland) and non-haemolysed capillary blood was collected for lactate measurement after the test (YSI Incorporated, USA). Subjects reported perceived exhaustion at peak exercise using the Borg scale.

In study number I subjects continued to run on the treadmill after work economy and lactate threshold measurements was complete (Technogym runrace, Italy). Subjects ran at 5.3 % inclination and the running speed was increased every minute until VO_{2max} was reached during 3 to 6 minutes. The test principles followed established standards for testing of aerobic power in humans [200], and the automated respiratory methods using the Metamax II portable metabolic test system and breath by breath measurements to determine VO_{2max} (Cortex Biophysik GmbH, Leipzig, Germany). The average of the three highest continuous 10 seconds measurements were used to determine VO_{2max}.

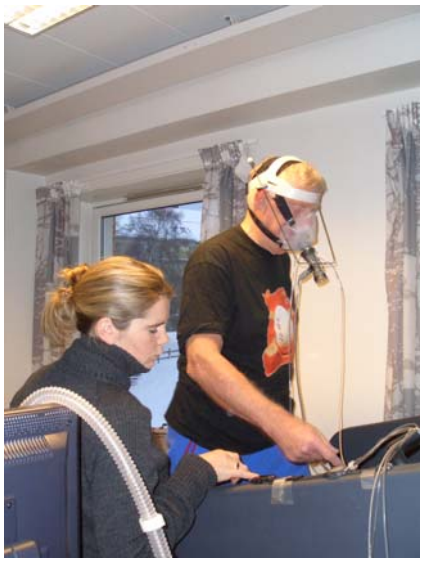
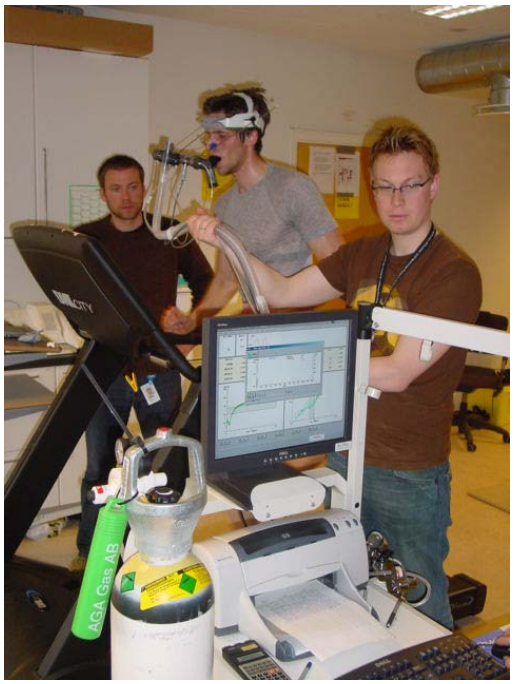


Figure 1. Testing of oxygen uptake

3.2 Cardiac output and stroke volume

Cardiac output was measured through study I-IV using the single breath gas technique to the Sensormedics Vmax Spectra 229 (SensorMedics Corp, California, USA). The test were initiated with a 10 minute warm up period on the treadmill followed by gradually increasing

work load until cardiac output were measured at 80-85% of VO_{2peak} in study II-IV and at speed corresponding to VO_{2max} in study I. When subjects reached the correct intensity they were instructed to start a breathing cycle with a complete emptying of the lungs followed by maximal inspiration of a gaseous mixture of 0.3% carbon monoxide, 0.3% acetylene, 0.3% methane, 20.9% oxygen balanced with 78.2% nitrogen, directly followed by one continuous expiration. In the solution acetylene serves as the soluble gas and methane the insoluble. The test method has previously been validated against the indirect Fick carbon dioxide rebreathing method and compared with open-circuit acetylene uptake, and found reliable and valid for measuring cardiac output. A coefficient of variation of 7.6% was found at a work load of 200W and the authors concluded that the single breath measurements requires a constant, slow exhalation rate making the procedure difficult to perform at the highest intensities [39].



Figur 2. Testing of peak stroke volume

3.3 Total blood- and plasma volume

The long slow distance and 4 x 4 minute interval training group in study number I, and the hyperoxic training group in study number III had the blood- and plasma volume determined through the Evans blue dye dilution technique before and after training [122]. Subjects rested 30 minute in a supine position before a venous catheter was inserted in the antecubital vein in the upper arm. A 6 ml venous blood sample was drawn, before approximately 2.5 ml of Evans blue dye was injected into the vein. A 3 ml blood sample was drawn into a sodium heparine vacutainer tube at 10, 20 and 30 minutes after the Evans blue dye injection to evaluate the

dilution of dye in the blood. After collection the vacutainer tubes were spun in an ultracentrifuge for 10 minutes at 3500 revolutions $\cdot$ min^{-1} (Kubota 2010, Japan). Plasma was transferred to a blank container and samples read in a spectrophotometer (Shimadzu UV-1601, Japan) at wavelengths 620 and 740 nm. Hematocrit was measured using a Cobas Micros CT16 (Bergman Instrumentering as, Norway), and blood volume estimated by dividing plasma volume by one minus hematocrit. Corrections for trapped plasma and peripheral sampling were performed [122].

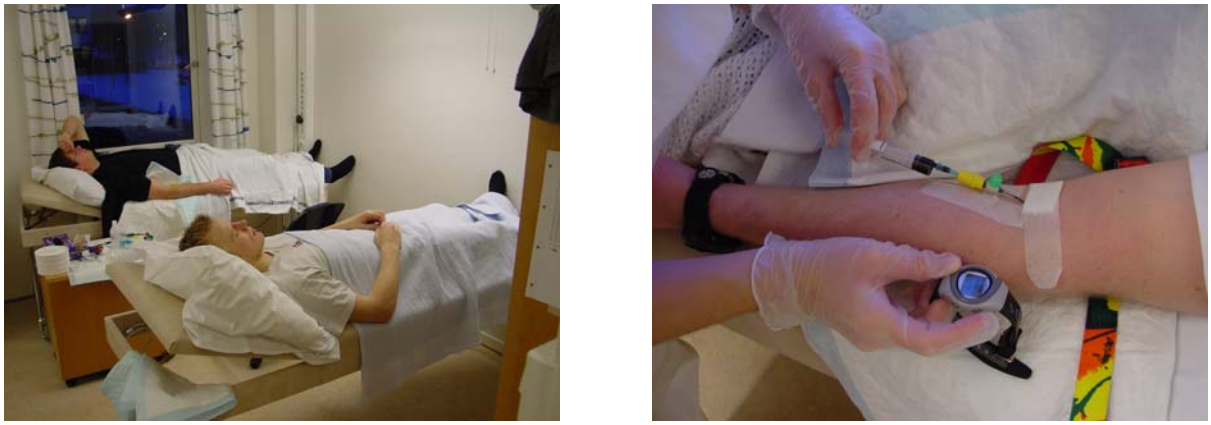


Figure 3. Testing of blood volume

3.4 Cardiovascular magnetic resonance

All patients in the endurance training group in study II underwent CMR examination before and after the training period using a Philips Intera® 1.5 T MR whole body scanner (Phillips, Best, Netherlands), equipped with a 5-element cardiac phased array coil and cardiac software package (R9.1.1). Breath-hold cine two-chamber, four-chamber and long-axis views were acquired using a retrospectively electrocardiographically gate steady state free procession (SSFP) breath-hold cine sequence. A stack of 10-mm thick contiguous slices encompassing the left ventricle from base to apex in the cardiac short-axis orientation was acquired for volumetric measurements. Imaging parameters included the following: 2.9/1.4 (repetition time ms/echo-time ms), 160 × 160 matrix, 320 × 320 mm field of view, 2.0 × 2.0 mm in-plane spatial resolution, half Fourier acquisition and 65-degree flip angle. A total of 30 heart phases were acquired. End diastolic volume (EDV), end systolic volume (ESV), left ventricular mass (LVM), stroke volume (SV), cardiac output (CO) and ejection fraction (EF) were measured by semiautomated segmentation of end-diastolic and end-systolic areas using dedicated software (Easyvision, Philips, Best, Netherlands) [91, 169]. Cardiac magnetic resonance stress testing allows for assessments of morphology and cardiac function and is a diagnostic tool for

coronary artery disease [32, 34]. The main concern with the use of cardiac magnetic resonance imaging is the motion of coronary arteries in the respiratory and cardiac cycle [165], however techniques for free breathing and correction through contrast agents and navigator techniques has been developed [169].

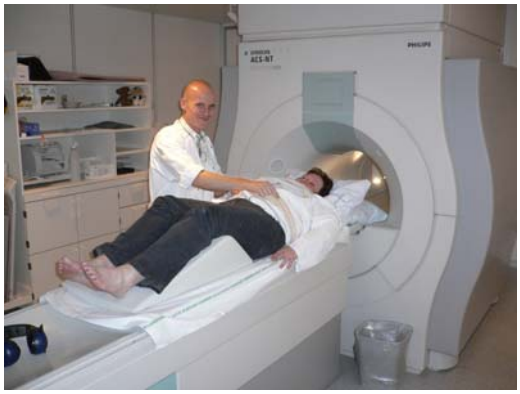


Figure 4. Magnetic resonance imaging

3.5 Maximal skeletal muscle strength

Maximal strength in the lower extremities was tested by 1RM in a dynamic horizontal leg press down to a knee joint angle of 90° using a horizontal leg press machine (Technogym, Italy) in study number IV. 1RM was obtained by repeating the leg press exercise with increasing loads of 5-10 kilogram until the subjects were not able to complete the lift. A total of 6-8 lifts were used to achieve 1RM and the highest weight lifted was recorded as 1RM.

3.6 Rate of force development

Maximal voluntary rate of force development and peak force during 90° dynamic leg press movement were assessed through a force platform (9286AA, Kistler, Switzerland) installed on the leg press machine (Technogym, Italy) in study number IV. Subjects performed 2 sets of dynamic leg press focusing on maximal force production with a resistance of 40 kilogram (kg). Data was collected at 2000 Hz (Bioware v3.06b, Kistler, Switzerland) and rate of force development was measured between 10-90% of peak force in the concentric phase of the leg press.

Figure 5. Testing of 1RM and rate of force development

3.7 Training Intervention

3.7.1 Interval training

Coronary artery disease patients in study II and III performed high aerobic intensity interval training through treadmill walking in a total of 30 interval training sessions. After 10 minutes of warm up, patients performed 4 x 4 minutes of aerobic intervals at 85-95% of the individual patients peak heart rate, corresponding to 80-90% of VO_{2peak}. 3 minutes active brakes were used in-between the high intensity periods at intensities corresponding to 65-75% of peak heart rate. Inclined treadmill walking were chosen due to 10-20% better performance during uphill walking and running compared to stationary biking [111], allowing for close control over intensity, patients well being and safety during training. Training intensity was chosen after documentation of the superiority of high aerobic intensity interval training compared with moderate intensity for increasing VO_{2peak} in coronary artery disease patients [153]. Heart rate was used as a control of training intensity, and the training load was increased whenever the heart rate was not maintained at the desired level during intervals. All training sessions were supervised to ensure training quality and patient safety, and no adverse events were reported during the studies. Individual training data such as walking speed, treadmill inclination, heart rate and Borg scale for perceived exhaustion was recorded in a training log, and the compliance of training was 29.6 ± 0.7 and 29.1 ± 1.1 training sessions in study II and III respectively.

Four different endurance training interventions were performed in study number I. All training sessions were performed running at a treadmill of 5.3% inclination. Training interventions 2-4 started with a 10 min warm up and ended with a 3 min warm down period at

70% of maximal heart rate. Subjects carried out three training sessions per week for eight weeks, a total of 24 sessions. The four training interventions included:

1. Low slow distance running (LSD): The first group performed a continuous run at 70% of maximal heart rate for 45 min
2. Lactate threshold running (LT): The second group performed a continuous run at lactate threshold at 85% of maximal heart rate for 24.25 minutes.
3. 15 x 15 seconds interval running (15x15s): The third group performed 47 repetitions of 15 s intervals at 90 to 95% of maximal heart rate with 15 seconds active resting-periods at warm up velocity, corresponding to 70% maximal heart rate between each interval.
4. 4 x 4 minute interval running (4x4 min): A fourth group trained 4 x 4 minutes interval training at 90-95% of maximal heart rate with 3 minutes active resting-periods at 70% of maximal heart rate between each interval.

Each training intervention was made equal in terms of energy consumption after an accurate calculation and a pilot study where active periods and warm up was included. On average the total oxygen uptake for the training protocols was 130 ± 15 Litre or approximately 650 Kcal per training session.

Figure 6. Hyperoxic high aerobic intensity interval training

3.7.2 Strength training

Coronary artery disease patients trained maximal strength training of the legs in study number IV. Patients met to training at the exercise physiology laboratory three times a week for 8 weeks completing a total of 24 strength training sessions. Each strength training session consisted of 5 minutes warm up of stationary biking and 4 series with 4 repetitions in each

series of horizontal dynamic leg press. Exercise was made with emphasis on maximal mobilization of force in the concentric action and subjects started the concentric movement when the knee angle corresponded to 90°. Subjects trained with a progressive work load of 85-90% of the individual 1RM. When subjects were able to perform more than four repetitions in a set, the load was increased by 2.5 kg. A 2 minutes rest period was employed between each set of exercise. The compliance of training was 23.8 ± 0.4 training sessions.

3.8 Statistical analysis

Statistical analyses were performed using the software program SPSS, version 11.0-14.0 (Statistical Package for Social Science, Chicago, USA). Table values are expressed as mean ± standard deviation (SD), while figure values are expressed as mean percentage change and data variability as standard error (SE). A two-tailed $p < 0.05$ was accepted as statistically significant for all tests. Q-Q plots were used to test data for normal distribution. Due to the relatively small sample size non parametric statistics tests were chosen in paper II-IV. Changes within groups were determined by the Wilcoxon signed ranks test, while differences between groups were calculated by using the Mann-Whitney U-test on delta changes from pre to post test. Relationships between variables were assessed with correlation analysis. In paper number I differences within and between groups was calculated through a two-way analysis of repeated measures ANOVA (least significance difference test) comparing means for continuous variables.

4 Summary of Results

Paper I. Aerobic High-Intensity Intervals Improve VO_{2max} More Than Moderate Training

The objectives of this study was to compare the effects of aerobic endurance training at different intensities- and methods matched for total work and frequency.

1. VO_{2max} increased by 5.5% in the 15/15 and by 7.2 % in the 4x4 group after training, with no difference in the training response between the 15/15 and 4x4 group.
2. No change in VO_{2max} was detected in the LT and LSD group.
3. Running economy significantly improved in all the training groups by 7.5-11.7%, but no difference was detected between groups.
4. Lactate threshold did not change in any of the groups when expressed as % VO_{2max}. Velocity at lactate threshold was however significantly improved by an average of 9.6% in all four groups as a consequence of change in running economy and VO_{2max}.
5. Stroke volume changed from pre to post training in the 15/15 and the 4x4 min group. No significant difference was observed between the two groups, however the smallest p value was detected in the 4 x 4 min group.
6. No significant haematological response to training was found.

Paper II. How to Improve Stroke Volume in Heart Patients

The objectives of this study was to investigate to which extent aerobic interval training at 85-95% of maximal heart rate improves peak stroke volume and myocardial ejection fraction in coronary artery disease patients.

1. Peak stroke volume significantly improved by 23% after interval training.
2. Resting left ventricle ejection fraction significantly improved by 5% after interval training.
3. Resting left ventricle end diastolic volume and myocardial weight as well as cardiac output was unchanged after training. There was a non-significant trend towards decreased end systolic volume and heart rate, as well as increased stroke volume.
4. VO_{2peak} significantly improved by 17% after high aerobic intensity interval training

Paper III. Aerobic interval training improve VO_{2peak} in heart patients; no additional effect from hyperoxia

The objectives of this study were to investigate if 100% oxygen supplementation during high aerobic intensity interval training improves training performance and VO_{2peak} in coronary artery disease patients.

1. VO_{2peak} improved 16% and 17% after 30 training session of high aerobic intensity interval training at 85-95% of peak heart rate in the hyperoxic- and normoxic training group respectively.
2. VO_{2peak} improved 0.53 and 0.57% per training session in the two training groups
3. VO_{2peak} was equal in hyperoxia (65% O_2) and normoxia (21% O_2) in the hyperoxic training group both before and after interval training.
4. Peak stroke volume increased significantly after high aerobic intensity interval training in both training groups.
5. Blood volume did not change after 10 weeks of hyperoxic interval training in the hyperoxic training group.
6. Quality of life improved in both training groups after interval training.

Paper IV. Strength Training Restores Walking in Heart Patients

The objectives of this study were to investigate the effect of maximal strength training of the legs has upon leg strength, rate of force development and walking mechanical efficiency in coronary artery disease patients.

1. Maximal strength in leg press measured through one repetition maximum increased by 44% after strength training.
2. This corresponds to an increase in strength by 1.6% per training session.
3. Maximal strength training increased rate of force development by 85%.
4. Maximal strength training increased peak force by 18%.
5. Maximal strength training increased walking efficiency by 35%.
6. Quality of life increased significant in the score for mental health after strength training.
7. Maximal strength training did not change total serum testosterone.

5 Discussion

The present thesis reports that high aerobic intensity training at 90-95% of maximal heart rate improves VO_{2max} and maximal cardiac stroke volume in healthy young men, whereas isocaloric training protocols at lower intensities does not result in any changes (I). High aerobic intensity interval training at 85-95% of peak heart rate improves VO_{2peak} and peak cardiac stroke volume in coronary artery disease patients to the same extent as healthy young men (II-III). Hyperoxic high aerobic intensity interval training gives no additional improvements in VO_{2peak} or peak cardiac stroke volume compared with normoxic training in coronary artery disease patients. Patients were oxygen demand limited in the skeletal muscles at VO_{2peak} during acute hyperoxic testing both before and after training (III). Maximal strength training of the legs enhances muscular strength and walking efficiency in coronary artery disease patients despite no change in VO_{2peak} (IV).

5.1 Improvements in maximal aerobic power

The present thesis confirms that the intensity of endurance training is the most important factor to improve maximal oxygen uptake (VO_{2max}) in healthy young men (I). This is also in line with previous studies in cardiovascular disease patients [153, 193]. The present thesis demonstrates and confirms that VO_{2max}, VO_{2peak} and performance increase significantly with high aerobic intensity interval training at 85-95% of peak heart rate. The increase in aerobic power is achieved after a few weeks of training, in both healthy men and coronary heart disease patients (I-III). In healthy young men only training intensities at 90-95% of maximal heart rate, performed after interval principles improved VO_{2max} (I). This differs from previous studies of coronary heart disease and heart failure patients, where long slow distance training at 70% of peak heart rate improved VO_{2peak} as well. The improvement in VO_{2peak} was however only half of the outcome from high aerobic intensity interval training [153, 193]. The VO_{2max} was higher in the healthy young men (I) compared with previous studies of cardiovascular disease patients [153, 193]. The mean VO_{2max} was between 55 and 60 $ml \cdot kg^{-1} \cdot min^{-1}$ in study number I, while mean VO_{2peak} ranged from ~13 $ml \cdot kg^{-1} \cdot min^{-1}$ [193] to ~31 $ml \cdot kg^{-1} \cdot min^{-1}$ [153] in previous studies of heart patients. The results may imply that low intensity endurance training may increase VO_{2max} when VO_{2max} is initially low. When choosing mode and intensity of endurance training the amount of improvement desired per training session, and the initial level of aerobic power might be considered before expectations of improvements are set.

High aerobic intensity interval training improves VO_{2peak} in coronary artery disease patients to a greater extent than VO_{2max} in healthy young men when expressed as percent improvement (I-III). VO_{2peak} increased by an average of 0.53-0.57% per training session in coronary artery disease patients. Half the improvement in VO_{2max} per training session was observed in healthy young men with an average of 0.23-0.30 % increase in VO_{2max}. The relative difference is due to the lower initial aerobic power observed in coronary artery disease patients. When comparing the absolute change in aerobic power surprisingly similar results are observed between studies. On average coronary artery disease patients improved VO_{2peak} by 4 $ml \cdot kg^{-1} \cdot min^{-1}$ and 4.5 $ml \cdot kg^{-1} \cdot min^{-1}$ in study II and III, respectively. In study number I, high aerobic intensity interval training by 15 x 15 seconds and 4 x 4 minutes improved VO_{2max} on average 3.9 $ml \cdot kg^{-1} \cdot min^{-1}$ and 4.9 $ml \cdot kg^{-1} \cdot min^{-1}$, respectively. Converted to improvement per training session, 0.13 $ml \cdot kg^{-1} \cdot min^{-1}$, 0.15 $ml \cdot kg^{-1} \cdot min^{-1}$, 0.16 $ml \cdot kg^{-1} \cdot min^{-1}$ and 0.20 $ml \cdot kg^{-1} \cdot min^{-1}$ was detected in study II, III and group 15x15 second and 4 x 4 minutes in study I, respectively. This implies that coronary artery disease patients through supervised training can perform high aerobic intensity interval training with equal quality as healthy young male subjects. So, despite documented coronary artery disease and myocardial insufficiency coronary artery disease patients achieve similar training outcomes as healthy young men when expressed as absolute values. The similarity in the training outcome between studies serves as an indication of the potential high intensity interval training possesses as long as it is performed aerobically. The equality in the training response might serve as an argument for incorporating high aerobic intensity interval training as part of recommendations for cardiovascular disease patients.

When considering the importance of high VO_{2peak} in association with mortality in cardiovascular disease patients [117] it should be noticed that high aerobic intensity interval training rapidly increases VO_{2peak} in a high mortality risk population. The mean increase in VO_{2peak} was approximately 4 – 4.5 $ml \cdot kg^{-1} \cdot min^{-1}$ after 30 interval training sessions in coronary artery disease patients (II-III). According to Myers et al. [117] a 1 MET (3.5 $ml \cdot kg^{-1} \cdot min^{-1}$) increase in aerobic power corresponds with a 12 % reduction in mortality risk. High aerobic intensity training thereby serves as a non pharmaceutical treatment, substantially reducing the risk of mortality in only a few weeks. In addition training might serve as a protective agent against further development of coronary artery disease [176], and improve risk factors related to cardiovascular disease [14, 175]. A large improvement in VO_{2peak} inflicted by high aerobic intensity interval training in a short period of time is both significant

and clinically meaningful for the patients. Training might appear motivational since patients quickly sense the effect of training in their daily life.

Current guidelines regarding training and health recommends 30 minutes of not necessarily structured, moderate exercise, preferably every day of the week to ensure health benefits [175]. The recommendation might be questioned in view of the result from the present thesis, and the importance of high aerobic power for reducing mortality [57, 113, 117]. One might argue that some elements of high aerobic intensity training are needed to ensure good health in both healthy subjects and coronary artery disease patients. This might be particular important in coronary artery disease patients with low initial VO_{2peak}, where significant improvements in fitness and risk of mortality might be obtained in just a few weeks of training (II-III). If a relationship exist between cardiovascular fitness and health aspects the fact that high aerobic intensity training improves VO_{2max} in healthy subjects is important to consider. According to the data from the present study (I), a young and healthy population would probably not experience any improvements in VO_{2max} following the recommendations from the present guidelines and training or activity would merely serve as a means of maintenance. High aerobic intensity training is reported to be twice as effective as low intensity training in improving VO_{2peak} in heart patients [153, 193]. In this population cardiovascular fitness has been proven vital for future development of the disease and life expectancy [58, 85]. With the important link between cardiovascular fitness and mortality risk high aerobic intensity interval training has the ability to quickly increase cardiopulmonary fitness and thereby health prospects as well.

Maximal strength training of the legs did not enhance VO_{2peak} in coronary artery disease patients (IV), however, as expected the work efficiency was improved. VO_{2max} is minimally effected by maximal strength training [94], however enhanced muscular strength may stimulate to increased voluntary endurance activity. With a limited VO_{2peak} in coronary artery disease patients, improvements in walking efficiency directly translate into similarly improved walking ability and performance.

5.2 Myocardial changes with training

In the present thesis high aerobic intensity interval training significantly improved peak stroke volume in both coronary artery disease patients and healthy young males (I-III). Peak stroke volume was initially higher in healthy young men compared with coronary artery disease

patients with mean values between ~130 and 155 ml · beat^{-1} in healthy young men and ~90 and 114 ml · beat^{-1} in coronary artery disease patients before training. Peak stroke volume improved relatively the most after training in coronary artery disease patients with ~ 15-17 % improvement (II-III) while healthy young men improved stroke volume by ~10% (I). The slightly larger percent increase in stroke volume observed in coronary artery disease patients after training compared to healthy young men, matches the larger percent improvement in aerobic power noted in coronary artery disease patients compared with healthy young men. The absolute delta values are however, as observed with VO_{2peak} and VO_{2max}, surprisingly equal between studies. Maximal stroke volume improve with ~14-15 ml · beat^{-1} and peak stroke volume by ~15-21 ml· beat^{-1} in healthy young men (I) and coronary artery disease patients (II-III), respectively. The improvement per interval training session was 0.58-0.63 ml · beat^{-1} and 0.51-0.70 ml · beat^{-1} in the healthy young men (I) and coronary artery disease patients, respectively (II-III). This implies that despite reduced initial stroke volume, reduced myocardial efficiency and documented ischemic heart disease, coronary artery disease patients have the same absolute myocardial response to high aerobic intensity interval training as healthy young men. High aerobic intensity interval training thereby seems to inflict the same shear stress on the cardiovascular system improving the oxygen supply to working skeletal muscles in both young healthy men and coronary artery disease patients. Stroke volume deterioration documented with aging and disease may thereby primary reflect increasing levels of inactivity, at least before ischemia and infarction may disrupt peak myocardial function.

High aerobic intensity interval training improved resting left ventricle ejection fraction in coronary artery disease patients (II). Improvements in peak stroke volume in coronary artery disease patients is probably due to increased myocardial contractility as observed with increased resting left ventricular ejection fraction. Improvements in resting left ventricular ejection fraction has previously been reported in old heart failure patients together with a reversal of left ventricle remodelling [193]. High aerobic intensity interval training did not change the left ventricle dimension, indicating that a larger dose of high aerobic intensity interval training might be needed to achieve the reported increase in left ventricle dimension observed in endurance trained female athletes [192]. In the present study (II), there was a trend toward decreased end systolic volume with a subsequent increase in stroke volume. Heart rate decreased correspondingly, maintaining an unchanged cardiac output. All those changes are concordant, indicating that the trend is real. In addition, the result was a

significant increase in resting ejection fraction, indicating an enhanced left ventricular systolic performance. Left ventricle ejection fraction and reversed myocardial remodelling normalizing myocardial size has been reported to be dependent of training intensity, with only aerobic interval training demonstrating changes in heart failure patients [193].

Training intensities below 85% of maximal heart rate did not improve maximal stroke volume or VO_{2max} in healthy young men (I). The present thesis thereby reports a dependency of training intensity in the effort to improve maximal stroke volume in healthy individuals. The effect of long slow distance training on peak stroke volume was not investigated in coronary artery disease patients in the present studies (II-III). Based on the similarities in the response in VO_{2peak} and peak stroke volume detected in healthy men and coronary artery disease patients, a logic deduction might be expecting peak stroke volume to follow the improvement in VO_{2peak} reported in the study by Rognmo et al. [153]. The effect of long slow distance training in their study was half that of high aerobic intensity training in coronary artery disease patients. The fact that stroke volume plateaus at different level of maximal heart rate [54, 196] may explain why high aerobic intensity training is needed to improve VO_{2max} and maximal stroke volume in healthy young men. When training at 90-95% of maximal heart rate the healthy young men train at the highest cardiac output they can maintain over 3-8 minutes influencing the cardiovascular system maximally. Training at a lower intensity may not inflict enough shear stress on the cardiovascular system due to training at a lower cardiac output. According to the data from Zhou et al. [196] and Gledhill et al. [54] cardiac patients with low initial VO_{2peak} reach peak cardiac output at a low percentage of maximal heart rate, thereby low intensity training may also increase peak stroke volume and VO_{2peak} in these patients as well [153].

The present thesis displays a differentiation in stroke volume response with endurance training intensity. Maximal or peak stroke volume in moderately trained healthy young men and coronary artery disease patients improve to a similar extent after high aerobic intensity interval training. This highlights the importance of training intensity in healthy subjects and particularly in coronary artery disease patients with already reduced myocardial function. The improvement in stroke volume seems to follow the changes in aerobic power in both healthy men and coronary artery disease patients. This indicates that myocardial function and skeletal muscle metabolism are closely matched and that training responses at the supply and demand level go hand in hand.

Maximal strength training with high load and focus upon maximal voluntary contraction does not change stroke volume or cardiac output in coronary artery disease patients (IV), therefore intensity dependent endurance training must be applied to achieve improvements in myocardial function. Strength training may however serve as an important means for better circulatory management and blood pressure control in coronary artery disease patients [104]. The present studies together with others [193] suggest that that coronary artery disease patients following the traditional part of official guidelines will not experience optimal coronary adaptations from training on a dysfunctional myocardium [193].

5.3 Demand and supply limitations to training

High aerobic intensity interval training increases the oxygen delivery to working skeletal muscles through elevated peak stroke volume in both healthy individuals and coronary artery disease patients (I-III). Peak stroke volume is elevated to the same extent as VO_{2max} or VO_{2peak} implying that the oxygen demand is at least on level with the supply of oxygen, but might be higher.

In coronary artery disease patients no acute effect of hyperoxia was found on VO_{2peak} and performance, despite significantly increased haemoglobin oxygen saturation. This observation indicates a demand limitation to oxygen consumption in the working skeletal muscles of the coronary artery disease patients at the inclusion point in the study (III). Oxygen supply often limits VO_{2max} in the healthy human skeletal muscles [92, 147-149, 157, 181], however metabolic limitations in VO_{2max} is suggested in unfit subjects [182]. Depressed oxidative capacity in the skeletal muscles of heart failure patients has been reported, implying that VO_{2peak} is limited by the oxidative capacity of mitochondria in the working muscles [41]. This is in agreement with the findings in the present study of coronary artery disease patients where 65% inspired oxygen had no effect on VO_{2peak} and performance. Some studies report increased VO_{2peak} and performance in coronary artery disease patients exposed to hyperoxia, while others do not observe changes in VO_{2peak} in line with the observations in paper number III [146, 154]. As discussed in the paper (III) several other factors not controlled for in the study, as vascular vasoconstriction restricting oxygen supply to the working skeletal muscles, or the level of myocardial ischemia affecting myocardial contractility may also have contributed to the lack of improvement in exercise performance. In addition it is important to note that the coronary artery disease patients did not suffer from exercise induced hypoxemia during peak normoxic exercise, thereby oxygen delivery was not initially limited in normoxia.

Endurance trained healthy men were not investigated during hyperoxic exposure thereby no conclusions may be drawn in that context.

Hyperoxic high aerobic intensity interval training gave no additional effect on performance outcome compared with normoxic training. The present study (III) report that 30 hyperoxic high aerobic intensity interval training sessions increases VO_{2peak} and peak stroke volume to the same extent as normoxic training. This implies that under both training environments there is an equal oxygen supplementation and use of oxygen in the energy converting process in the working skeletal muscles. Thereby an equal training load was performed during both hyperoxic and normoxic training, and no additional shear stress was initiated to the cardiovascular system during hyperoxic training. The result is an equal high peak stroke volume and VO_{2peak} response between the two training groups.

Further investigations may reveal if hyperoxia is beneficial in severely ischemic coronary artery disease patients with ischemic coronary contractile restrictions. The present study (III) demonstrates that a VO_{2peak} below 35 ml $\cdot$ kg^{-1} $\cdot$ min^{-1} is associated with a metabolic skeletal muscle demand limitation in coronary artery disease patients. VO_{2peak} above this level might be needed before the limitations to exercise is switched from oxygen demand towards oxygen supply limitations. The present data (III) is in line with other studies were hyperoxic endurance training is reported to have no additional effect on VO_{2max}, even with higher VO_{2max} values reported in the subjects participating [134, 140]. The practical implication from the present study (III) is that mildly ischemic coronary artery disease patients does not benefit from hyperoxic supplementation during training and that thirty high aerobic intensity interval training sessions did not seem to be enough to switch from oxygen demand to oxygen supply limitation to exercise, thereby aerobic interval training can safely be performed in normoxia with equally high performance outcome.

5.4 Maximal strength training

Maximal strength training focusing on heavy loads, maximal voluntary contraction and few repetitions improves muscle strength and muscular contractility in coronary artery disease patients (IV), in line with other patient groups [75] and healthy subjects [72, 74]. Maximal strength training was well managed by the coronary artery disease patients and no adverse events were reported during strength training (IV). Improved muscle strength is important in many contexts, one being the occurrence of muscle atrophy and muscle weakness in coronary

patients [180], another muscular strength as a predictor of survival and the aggravation of muscle metabolism and skeletal muscle function with progressing New York Heart Association grading [10, 79, 189]. Thirdly low muscle strength is associated with high levels of disability in heart disease patients, reporting higher levels of disability than healthy age matched individuals [138], together with the loss of independence [40]. Low skeletal muscular strength and exercise impairment is reported to be due to skeletal muscular defects rather than limitations from the heart disease itself [109]. The advantage of maximal strength training is a rapid increase in skeletal muscular strength without any gain in body weight. Increased skeletal muscular strength renders the possibility to reduce disability and move the threshold of daily activities further away from 1RM. Another positive effect is enhanced level of daily activity, positively affecting cardiopulmonary fitness. Supervised training has the potential to reverse the fear of being physical active in this patient group [120]. Increased muscular strength is especially important in heart patients since increasing 1RM attenuates the circulatory response giving better circulatory management in day to day activities [104].

Maximal strength training increases the rate of force development in coronary artery disease patients (III), to the same extent as healthy subjects [72], and COPD patients [75]. The rate of force development is important in terms of the ability to rapidly develop force in the skeletal muscles, and contribute to better walking, stair climbing and prevents falls [16, 51, 94, 171]. Increased skeletal muscle strength through neural adaptations reported as increased rate of force development makes large increases in muscle strength feasible without increasing body weight, and are together with improved walking performance an indication of the importance of training both the neurological and the morphological aspects of the muscle [171]. Increased muscular strength could mean shifting the load of daily activity from heavy, to tolerable and repeatable [103], and the present study (III) demonstrates that a large increase in muscular strength is possible through maximal strength training, without any adverse events, and minimal time spent exercising. The importance of maximal strength training is highlighted even more through its effect on endurance performance in coronary artery disease patients.

Maximal strength training did not change serum testosterone concentration in coronary artery disease patients (IV). The coronary artery disease patients already within the laboratory normal range systemic testosterone levels did not change testosterone levels in response to training. Low testosterone levels have been reported in connection with cardiovascular disease [172], and the use of testosterone supplementation has been discussed in this patient

group. In the present thesis training did not affect serum testosterone concentration and thereby cannot at the present time be recommended as an alternative to testosterone supplementation in cardiovascular disease populations with low testosterone levels.

5.5 Walking efficiency and running economy

Maximal strength training affects endurance performance in addition to improving skeletal muscular strength and contractility. In coronary artery disease patients submaximal walking efficiency is reduced [78], but returns to the level of healthy age matched adults after 8 weeks of maximal strength training (IV). Maximal strength training improves walking mechanical efficiency considerably by 35% after only 24 training sessions. Strength training as part of rehabilitation of coronary artery diseases has the past years received more focus, after periods with endurance training primarily receiving attention [22]. This study verifies the importance of integrating maximal strength training in a rehabilitation setting since coronary artery disease patients gains a substantial strength and endurance outcome through a minimal training effort. This might prove very important for coronary artery disease patients whom due to the fear of the consequences of the disease often are inactive and thereby develops reduced skeletal muscle function and reduced physical capacity [109]. Improvements in submaximal endurance performance may stimulate to increased level of voluntary endurance activity at a higher intensity and increase the total daily energy expenditure [5], an important aspect in further development or regression of coronary artery disease [64]. Also increased skeletal muscular strength gives better management of daily living and increase the independence of elderly coronary artery disease patients [6]. Increasing the daily activity level has the potential to decrease the progression of the cardiovascular disease and improve the mortality risk due to increased maximal oxygen uptake [117, 121, 124]. In addition increased skeletal muscular strength and endurance performance improves physical function [28], and has the potential to better circulatory management in day to day activities [104]. Coronary artery disease patients are limited in their ability to walk [78] and report higher levels of disability that healthy age matched individuals [138]. Maximal strength training may thereby be necessary to imply to increase skeletal muscle strength and physical function [28] before patients are able to perform endurance training activities. Strength training has been reported to lower risk factors associated with coronary artery disease [15, 81] most likely through increased activity levels. Combining maximal strength training and aerobic interval training may even produce a larger training outcome of the endurance training due to improved submaximal and maximal endurance performance.

Improvements in work economy was also detected after long slow distance training, lactate threshold, 15 x 15 second and 4 x 4 minutes interval training in healthy young men (I). The improvement in work economy was approximately 5% in all groups. Work economy improved independent of improvements in VO_{2max}, demonstrating that running economy is not affected by the running speed used during training [68, 69]. No significant change in lactate threshold was detected in the present study when expressed as percent VO_{2max} however the lactate threshold running speed was improved on average by 9.6% in all the groups. Improved running speed is to be expected due to increased running economy in all training groups.

5.6 Blood volume

Blood volume was unchanged after high and low intensity endurance training in healthy young men (I), or after hyperoxic high aerobic intensity interval training in coronary artery disease patients (III). In study number I, mean blood volume ranged from 5.8 to 6.1 litres, while an average of 4.3 litres was measured in coronary artery disease patients in study III. Elevated blood volume has been observed in endurance trained individuals and physically active elderly [86, 168]. A low blood volume is associated with aging, a sedentary lifestyle and is found in medicated chronic heart failure patients [38, 49, 86]. A lower VO_{2peak}, higher age and the presence of coronary artery disease separated subjects in study III from study number I. Thereby cardiovascular disease, medication, age and inactivity in the cardiovascular disease patients compared with healthy young men may explain the initial difference in blood volume between studies. In addition two women participating in the cardiovascular disease study (III) might lower blood volume in this group compared with just male participants in study number I. No change in blood volume was detected as a result of endurance training in the present thesis (study I & III), neither after long slow distance training or high aerobic intensity interval training (I). Increased blood and plasma volume has been found in some studies after aerobic exercise training [118, 183], but not in others [26].

Blood volume may already have been well expanded before training for both the studies (I & III), reflecting that normal levels of daily activity may be enough to maintain blood volume. In the present investigations no long term data can explain the difference in blood volume between the studies, however data might serve as an indication for an age or disease related reduction in blood volume in cardiovascular disease patients. The amount of blood volume is important for circulatory distribution of oxygen and a reduced blood volume might affect

endurance performance negatively. The present training interventions does not improve blood volume thereby its effect on circulation and oxygen delivery cannot contribute in the explanation of the improvements in VO_{2max} and VO_{2peak} as a result of endurance training. At the present time the described training interventions cannot be recommended as a means for improving blood volume, although effects from longer periods of training cannot be ruled out.

5.7 Quality of life

In the studies of coronary artery disease patients aspects of measured quality of life was improved both due to high aerobic intensity interval training and maximal strength training. The improvement in quality of life is essential due to its clinical importance [177], connection with improved coronary functional class score [46, 63] and self reported disability [190]. Both improvements in VO_{2peak} (II-III), maximal muscular strength and walking efficiency (IV) improves quality of life, implying that several training interventions has the potential to affect physical and mental well being and thereby improve daily functionality and abilities.

5.8 Training is medicine

The present thesis demonstrates that supervised high aerobic intensity interval training result in an equally high training outcome in VO_{2peak} or VO_{2max} in coronary artery disease patients and healthy young men, and that training improves the blood supply to the exercising skeletal muscles through a larger cardiac stroke volume. Training as treatment of coronary artery disease affects further disease development, mortality, reduces the rate of rehospitalisation and improve overall heath status [184]. Training has the potential to reduce the cost of pharmaceuticals and correct the reduced physical state and function many coronary artery disease patients often find themselves in, inspite of modern medical treatment [138, 177, 197]. In addition both endurance and maximal strength training may be performed in coronary artery disease patients the same way as in healthy individuals without any adverse effects.

6 Conclusions

High aerobic intensity interval training was more effective than continues training with low to moderate intensity in improving maximal oxygen uptake in healthy young men. Maximal stroke volume improved due to high aerobic intensity interval training only.

High aerobic intensity interval training at 85-95% of peak heart rate significantly improved peak stroke volume and resting left ventricular ejection fraction in coronary artery disease patients.

Coronary artery disease patients showed peripheral limitations in peak oxygen uptake both before and after 10 weeks of hyperoxic training, thereby hyperoxic training did not improve the effect of the training over normoxia.

Maximal leg press exercise focusing on few repetitions with heavy load and maximal concentric contractions improved maximal strength, rate of force development, walking mechanical efficiency and thus walking performance capacity in coronary artery disease patients through a minimal exercise effort.

7 References

1. Abinader EG, Sharif DS, and Goldhammer E. Effects of low altitude on exercise performance in patients with congestive heart failure after healing of acute myocardial infarction. *Am J Cardiol* 1999; 83: 383-387

2. Ades PA. Cardiac rehabilitation and secondary prevention of coronary heart disease. *N Engl J Med* 2001; 345: 892-902

3. Ades PA, Ballor DL, Ashikaga T, Utton JL, and Nair KS. Weight training improves walking endurance in healthy elderly persons. *Ann Intern Med* 1996; 124: 568-572

4. Ades PA, Huang D, and Weaver SO. Cardiac rehabilitation participation predicts lower rehospitalization costs. *Am Heart J* 1992; 123: 916-921

5. Ades PA, Savage PD, Brochu M, Tischler MD, Lee NM, and Poehlman ET. Resistance training increases total daily energy expenditure in disabled older women with coronary heart disease. *J Appl Physiol* 2005; 98: 1280-1285

6. Ades PA, Savage PD, Cress ME, Brochu M, Lee NM, and Poehlman ET. Resistance training on physical performance in disabled older female cardiac patients. *Med Sci Sports Exerc* 2003; 35: 1265-1270

7. Almasbakk B and Hoff J. Coordination, the determinant of velocity specificity? *J Appl Physiol* 1996; 81: 2046-2052

8. American college of sports medicine position stand. Exercise for patients with coronary artery disease. *Med Sci Sports Exerc* 1994; 26: i-v

9. Andersen P and Saltin B. Maximal perfusion of skeletal muscle in man. *J Physiol* 1985; 366: 233-249

10. Anker SD, Swan JW, Volterrani M, Chua TP, Clark AL, Poole-Wilson PA, and Coats AJ. The influence of muscle mass, strength, fatigability and blood flow on exercise capacity in cachectic and non-cachectic patients with chronic heart failure. *Eur Heart J* 1997; 18: 259-269

11. Arbab-Zadeh A, Dijk E, Prasad A, Fu Q, Torres P, Zhang R, Thomas JD, Palmer D, and Levine BD. Effect of aging and physical activity on left ventricular compliance. *Circulation* 2004; 110: 1799-1805

12. Arena R, Myers J, Williams MA, Gulati M, Kligfield P, Balady GJ, Collins E, and Fletcher G. Assessment of functional capacity in clinical and research settings: A scientific statement from the american heart association committee on exercise, rehabilitation, and prevention of the council on clinical cardiology and the council on cardiovascular nursing. *Circulation* 2007; 116: 329-343

13. Bader DS, Maguire TE, Spahn CM, O'Malley CJ, and Balady GJ. Clinical profile and outcomes of obese patients in cardiac rehabilitation stratified according to national heart, lung, and blood institute criteria. *J Cardiopulm Rehabil* 2001; 21: 210-217

14. Balady GJ, Williams MA, Ades PA, Bittner V, Comoss P, Foody JA, Franklin B, Sanderson B, and Southard D. Core components of cardiac rehabilitation/secondary prevention programs: 2007 update: A scientific statement from the american heart association exercise, cardiac rehabilitation, and prevention committee, the council on clinical cardiology; the councils on cardiovascular nursing, epidemiology and prevention, and nutrition, physical activity, and metabolism; and the american association of cardiovascular and pulmonary rehabilitation. *J Cardiopulm Rehabil Prev* 2007; 27: 121-129

15. Banz WJ, Maher MA, Thompson WG, Bassett DR, Moore W, Ashraf M, Keefer DJ, and Zemel MB. Effects of resistance versus aerobic training on coronary artery disease risk factors. *Exp Biol Med (Maywood)* 2003; 228: 434-440

16. Bassey EJ, Fiatarone MA, O'Neill EF, Kelly M, Evans WJ, and Lipsitz LA. Leg extensor power and functional performance in very old men and women. *Clin Sci (Lond)* 1992; 82: 321-327

17. Behm DG. Neuromuscular implications and applications of resistance training. *Journal of Strength and Conditioning Research* 1995; 9: 264-274

18. Behm DG and Sale DG. Intended rather than actual movement velocity determines velocity-specific training response. *J Appl Physiol* 1993; 74: 359-368

19. Belardinelli R, Georgiou D, Cianci G, and Purcaro A. Randomized, controlled trial of long-term moderate exercise training in chronic heart failure: Effects on functional capacity, quality of life, and clinical outcome. *Circulation* 1999; 99: 1173-1182

20. Belardinelli R, Georgiou D, Ginzton L, Cianci G, and Purcaro A. Effects of moderate exercise training on thallium uptake and contractile response to low-dose dobutamine of dysfunctional myocardium in patients with ischemic cardiomyopathy. *Circulation* 1998; 97: 553-561

21. Bemben MG, Massey BH, Bemben DA, Misner JE, and Boileau RA. Isometric muscle force production as a function of age in healthy 20- to 74-yr-old men. *Med Sci Sports Exerc* 1991; 23: 1302-1310

22. Bjarnason-Wehrens B, Mayer-Berger W, Meister ER, Baum K, Hambrecht R, and Gielen S. Recommendations for resistance exercise in cardiac rehabilitation. Recommendations of the german federation for cardiovascular prevention and rehabilitation. *Eur J Cardiovasc Prev Rehabil* 2004; 11: 352-361

23. Blair SN, Kohl HW, 3rd, Paffenbarger RS, Jr., Clark DG, Cooper KH, and Gibbons LW. Physical fitness and all-cause mortality. A prospective study of healthy men and women. *Jama* 1989; 262: 2395-2401

24. Boutcher SH, McLaren PF, Cotton Y, and Boutcher Y. Stroke volume response to incremental submaximal exercise in aerobically trained, active, and sedentary men. *Can J Appl Physiol* 2003; 28: 12-26

25. Bouvier F, Saltin B, Nejat M, and Jensen-Urstad M. Left ventricular function and perfusion in elderly endurance athletes. *Med Sci Sports Exerc* 2001; 33: 735-740

26. Branch JD, 3rd, Pate RR, Bourque SP, Convertino VA, Durstine JL, and Ward DS. Exercise training and intensity does not alter vascular volume responses in women. *Aviat Space Environ Med* 1999; 70: 1070-1076

27. Brochu M, Poehlman ET, and Ades PA. Obesity, body fat distribution, and coronary artery disease. *J Cardiopulm Rehabil* 2000; 20: 96-108

28. Brochu M, Savage P, Lee M, Dee J, Cress ME, Poehlman ET, Tischler M, and Ades PA. Effects of resistance training on physical function in older disabled women with coronary heart disease. *J Appl Physiol* 2002; 92: 672-678

29. Brooks GA FT, White TP, Baldwin KM. *Exercise physiology. Human bioenergetics and its applications* Mayfield Publishing company Mountain View 2000

30. Buller NP, Jones D, and Poole-Wilson PA. Direct measurement of skeletal muscle fatigue in patients with chronic heart failure. *Br Heart J* 1991; 65: 20-24

31. Bunc V and Heller J. Energy cost of running in similarly trained men and women. *Eur J Appl Physiol Occup Physiol* 1989; 59: 178-183

32. Burgstahler C, Kunze M, Gawaz MP, Rasche V, Wohrle J, Hombach V, and Merkle N. Adenosine stress first pass perfusion for the detection of coronary artery disease in patients with aortic stenosis: A feasibility study. *Int J Cardiovasc Imaging* 2008; 24: 195-200

33. Byrnes WC, Mihevic PM, Freedson PS, and Horvath SM. Submaximal exercise quantified as percent of normoxic and hyperoxic maximum oxygen uptakes. *Med Sci Sports Exerc* 1984; 16: 572-577

34. Cheng AS, Pegg TJ, Karamitsos TD, Searle N, Jerosch-Herold M, Choudhury RP, Banning AP, Neubauer S, Robson MD, and Selvanayagam JB. Cardiovascular magnetic resonance perfusion imaging at 3-tesla for the detection of coronary artery disease: A comparison with 1.5-tesla. *J Am Coll Cardiol* 2007; 49: 2440-2449

35. Church TS, Lavie CJ, Milani RV, and Kirby GS. Improvements in blood rheology after cardiac rehabilitation and exercise training in patients with coronary heart disease. *Am Heart J* 2002; 143: 349-355

36. Clausen JP and Trap-Jensen J. Heart rate and arterial blood pressure during exercise in patients with angina pectoris. Effects of training and of nitroglycerin. *Circulation* 1976; 53: 436-442

37. Cohen MV. Myocardial ischemia is not a prerequisite for the stimulation of coronary collateral development. *Am Heart J* 1993; 126: 847-855

38. Davy KP and Seals DR. Total blood volume in healthy young and older men. *J Appl Physiol* 1994; 76: 2059-2062

39. Dibski DW, Smith DJ, Jensen R, Norris SR, and Ford GT. Comparison and reliability of two non-invasive acetylene uptake techniques for the measurement of cardiac output. *Eur J Appl Physiol* 2005; 94: 670-680

40. Doherty TJ. Invited review: Aging and sarcopenia. *J Appl Physiol* 2003; 95: 1717-1727

41. Drexler H, Riede U, Munzel T, Konig H, Funke E, and Just H. Alterations of skeletal muscle in chronic heart failure. *Circulation* 1992; 85: 1751-1759

42. Edwards WF, BD; Iyrilboz, Y; Dodd, SL. 29 physiological and expense implications of ptca rehabilitation. *Medicine & Science in Sports & Exercise* 1990; 22: S5

43. Ehsani AA. Mechanisms responsible for enhanced stroke volume after exercise training in coronary heart disease. *Eur Heart J* 1987; 8 Suppl G: 9-14

44. Ehsani AA, Biello DR, Schultz J, Sobel BE, and Holloszy JO. Improvement of left ventricular contractile function by exercise training in patients with coronary artery disease. *Circulation* 1986; 74: 350-358

45. Ekblom B, Huot R, Stein EM, and Thorstensson AT. Effect of changes in arterial oxygen content on circulation and physical performance. *J Appl Physiol* 1975; 39: 71-75

46. Erbs S, Linke A, Gielen S, Fiehn E, Walther C, Yu J, Adams V, Schuler G, and Hambrecht R. Exercise training in patients with severe chronic heart failure: Impact on left ventricular performance and cardiac size. A retrospective analysis of the leipzig heart failure training trial. *Eur J Cardiovasc Prev Rehabil* 2003; 10: 336-344

47. Erikssen G. Physical fitness and changes in mortality: The survival of the fittest. *Sports Med* 2001; 31: 571-576

48. Featherstone JF, Holly RG, and Amsterdam EA. Physiologic responses to weight lifting in coronary artery disease. *Am J Cardiol* 1993; 71: 287-292

49. Feigenbaum MS, Welsch MA, Mitchell M, Vincent K, Braith RW, and Pepine CJ. Contracted plasma and blood volume in chronic heart failure. *J Am Coll Cardiol* 2000; 35: 51-55

50. Ferguson S, Gledhill N, Jamnik VK, Wiebe C, and Payne N. Cardiac performance in endurance-trained and moderately active young women. *Med Sci Sports Exerc* 2001; 33: 1114-1119

51. Fleming BE, Wilson DR, and Pendergast DR. A portable, easily performed muscle power test and its association with falls by elderly persoms. *Arch Phys Med Rehabil* 1991; 72: 886-889

52. Frontera WR, Meredith CN, O'Reilly KP, Knuttgen HG, and Evans WJ. Strength conditioning in older men: Skeletal muscle hypertrophy and improved function. *J Appl Physiol* 1988; 64: 1038-1044

53. Gielen S, Schuler G, and Hambrecht R. Exercise training in coronary artery disease and coronary vasomotion. *Circulation* 2001; 103: E1-6

54. Gledhill N, Cox D, and Jamnik R. Endurance athletes' stroke volume does not plateau: Major advantage is diastolic function. *Med Sci Sports Exerc* 1994; 26: 1116-1121

55. Goldspink G. Cellular and molecular aspects of adaptation in skeletal muscle. in Komi P: Strength and power in sport. London Blackwell Scientific Publications; 1992. 211-229

56. Gonzalez-Alonso J, Richardson RS, and Saltin B. Exercising skeletal muscle blood flow in humans responds to reduction in arterial oxyhaemoglobin, but not to altered free oxygen. *J Physiol* 2001; 530: 331-341

57. Gulati M, Pandey DK, Arnsdorf MF, Lauderdale DS, Thisted RA, Wicklund RH, Al-Hani AJ, and Black HR. Exercise capacity and the risk of death in women: The st james women take heart project. *Circulation* 2003; 108: 1554-1559

58. Hagberg JM. Physiologic adaptations to prolonged high-intensity exercise training in patients with coronary artery disease. *Med Sci Sports Exerc* 1991; 23: 661-667

59. Hakkinen K, Alen M, Kallinen M, Newton RU, and Kraemer WJ. Neuromuscular adaptation during prolonged strength training, detraining and re-strength-training in middle-aged and elderly people. *Eur J Appl Physiol* 2000; 83: 51-62

60. Hakkinen K, Kallinen M, Izquierdo M, Jokelainen K, Lassila H, Malkia E, Kraemer WJ, Newton RU, and Alen M. Changes in agonist-antagonist emg, muscle csa, and force during strength training in middle-aged and older people. *J Appl Physiol* 1998; 84: 1341-1349

61. Hambrecht R, Adams V, Erbs S, Linke A, Krankel N, Shu Y, Baither Y, Gielen S, Thiele H, Gummert JF, Mohr FW, and Schuler G. Regular physical activity improves endothelial function in patients with coronary artery disease by increasing phosphorylation of endothelial nitric oxide synthase. *Circulation* 2003; 107: 3152-3158

62. Hambrecht R, Fiehn E, Weigl C, Gielen S, Hamann C, Kaiser R, Yu J, Adams V, Niebauer J, and Schuler G. Regular physical exercise corrects endothelial dysfunction and improves exercise capacity in patients with chronic heart failure. *Circulation* 1998; 98: 2709-2715

63. Hambrecht R, Gielen S, Linke A, Fiehn E, Yu J, Walther C, Schoene N, and Schuler G. Effects of exercise training on left ventricular function and peripheral resistance in patients with chronic heart failure: A randomized trial. *Jama* 2000; 283: 3095-3101

64. Hambrecht R, Niebauer J, Marburger C, Grunze M, Kalberer B, Hauer K, Schlierf G, Kubler W, and Schuler G. Various intensities of leisure time physical activity in patients with coronary artery disease: Effects on cardiorespiratory fitness and progression of coronary atherosclerotic lesions. *J Am Coll Cardiol* 1993; 22: 468-477

65. Hambrecht R, Walther C, Mobius-Winkler S, Gielen S, Linke A, Conradi K, Erbs S, Kluge R, Kendziorra K, Sabri O, Sick P, and Schuler G. Percutaneous coronary angioplasty compared with exercise training in patients with stable coronary artery disease: A randomized trial. *Circulation* 2004; 109: 1371-1378

66. Hambrecht R, Wolf A, Gielen S, Linke A, Hofer J, Erbs S, Schoene N, and Schuler G. Effect of exercise on coronary endothelial function in patients with coronary artery disease. *N Engl J Med* 2000; 342: 454-460

67. Haskell WL, Alderman EL, Fair JM, Maron DJ, Mackey SF, Superko HR, Williams PT, Johnstone IM, Champagne MA, Krauss RM, and et al. Effects of intensive multiple risk factor reduction on coronary atherosclerosis and clinical cardiac events in men and women with coronary artery disease. The stanford coronary risk intervention project (scrip). *Circulation* 1994; 89: 975-990

68. Helgerud J. Maximal oxygen uptake, anaerobic threshold and running economy in women and men with similar performances level in marathons. *Eur J Appl Physiol Occup Physiol* 1994; 68: 155-161

69. Helgerud J, Engen LC, Wisloff U, and Hoff J. Aerobic endurance training improves soccer performance. *Med Sci Sports Exerc* 2001; 33: 1925-1931

70. Hickson RC, Dvorak BA, Gorostiaga EM, Kurowski TT, and Foster C. Potential for strength and endurance training to amplify endurance performance. *J Appl Physiol* 1988; 65: 2285-2290

71. Hickson RC, Foster C, Pollock ML, Galassi TM, and Rich S. Reduced training intensities and loss of aerobic power, endurance, and cardiac growth. *J Appl Physiol* 1985; 58: 492-499

72. Hoff J, Gran A, and Helgerud J. Maximal strength training improves aerobic endurance performance. *Scand J Med Sci Sports* 2002; 12: 288-295

73. Hoff J and Helgerud J. Endurance and strength training for soccer players: Physiological considerations. *Sports Med* 2004; 34: 165-180

74. Hoff J, Helgerud J, and Wisloff U. Maximal strength training improves work economy in trained female cross-country skiers. *Med Sci Sports Exerc* 1999; 31: 870-877

75. Hoff J, Tjonna AE, Steinshamn S, Hoydal M, Richardson RS, and Helgerud J. Maximal strength training of the legs in copd: A therapy for mechanical inefficiency. *Med Sci Sports Exerc* 2007; 39: 220-226

76. Hoppeler H and Weibel ER. Limits for oxygen and substrate transport in mammals. *J Exp Biol* 1998; 201: 1051-1064

77. Horvat M, Yoshida S, Prakash R, Marcus HS, Swan HJ, and Ganz W. Effect of oxygen breathing on pacing-induced angina pectoris and other manifestations of coronary insufficiency. *Circulation* 1972; 45: 837-844

78. Hoydal KL, Helgerud J, Karlsen T, Stoylen A, Steinshamn S, and Hoff J. Patients with coronary artery- or chronic obstructive pulmonary disease walk with mechanical inefficiency. *Scand Cardiovasc J* 2007: 1-6

79. Hulsmann M, Quittan M, Berger R, Crevenna R, Springer C, Nuhr M, Mortl D, Moser P, and Pacher R. Muscle strength as a predictor of long-term survival in severe congestive heart failure. *Eur J Heart Fail* 2004; 6: 101-107

80. Hunter GR, McCarthy JP, and Bamman MM. Effects of resistance training on older adults. *Sports Med* 2004; 34: 329-348

81. Hurley BF, Hagberg JM, Goldberg AP, Seals DR, Ehsani AA, Brennan RE, and Holloszy JO. Resistive training can reduce coronary risk factors without altering vo2max or percent body fat. *Med Sci Sports Exerc* 1988; 20: 150-154

82. Izquierdo M, Aguado X, Gonzalez R, Lopez JL, and Hakkinen K. Maximal and explosive force production capacity and balance performance in men of different ages. *Eur J Appl Physiol Occup Physiol* 1999; 79: 260-267

83. Izquierdo M, Hakkinen K, Ibanez J, Anton A, Garrues M, Ruesta M, and Gorostiaga EM. Effects of strength training on submaximal and maximal endurance performance capacity in middle-aged and older men. *J Strength Cond Res* 2003; 17: 129-139

84. Izquierdo M, Ibanez J, Gorostiaga E, Garrues M, Zuniga A, Anton A, Larrion JL, and Hakkinen K. Maximal strength and power characteristics in isometric and dynamic actions of the upper and lower extremities in middle-aged and older men. *Acta Physiol Scand* 1999; 167: 57-68

85. Jae SY, Carnethon MR, Heffernan KS, Choi YH, Lee MK, and Fernhall B. Association between cardiorespiratory fitness and prevalence of carotid atherosclerosis among men with hypertension. *Am Heart J* 2007; 153: 1001-1005

86. Jones PP, Davy KP, DeSouza CA, van Pelt RE, and Seals DR. Absence of age-related decline in total blood volume in physically active females. *Am J Physiol* 1997; 272: H2534-2540

87. Joyner MJ and Coyle EF. Endurance exercise performance: The physiology of champions. *J Physiol* 2008; 586: 35-44

88. Karlsdottir AE, Foster C, Porcari JP, Palmer-McLean K, White-Kube R, and Backes RC. Hemodynamic responses during aerobic and resistance exercise. *J Cardiopulm Rehabil* 2002; 22: 170-177

89. Kasch FW, Boyer JL, Van Camp S, Nettl F, Verity LS, and Wallace JP. Cardiovascular changes with age and exercise. A 28-year longitudinal study. *Scand J Med Sci Sports* 1995; 5: 147-151

90. Kendziorra K, Walther C, Foerster M, Mobius-Winkler S, Conradi K, Schuler G, Sabri O, Hambrecht R, and Kluge R. Changes in myocardial perfusion due to physical exercise in patients with stable coronary artery disease. *Eur J Nucl Med Mol Imaging* 2005; 32: 813-819

91. Kim WY, Stuber M, Bornert P, Kissinger KV, Manning WJ, and Botnar RM. Three-dimensional black-blood cardiac magnetic resonance coronary vessel wall imaging detects positive arterial remodeling in patients with nonsignificant coronary artery disease. *Circulation* 2002; 106: 296-299

92. Knight DR, Schaffartzik W, Poole DC, Hogan MC, Bebout DE, and Wagner PD. Effects of hyperoxia on maximal leg o2 supply and utilization in men. *J Appl Physiol* 1993; 75: 2586-2594

93. Komi PV. *Strength and power in sports* Blackwell Scientific Publications, Oxford 1992

94. Komi PV. *Strength and power in sport.* Blackwell Publishing Oxford 2003

95. Larsson L, Sjodin B, and Karlsson J. Histochemical and biochemical changes in human skeletal muscle with age in sedentary males, age 22--65 years. *Acta Physiol Scand* 1978; 103: 31-39

96. Levine BD. : What do we know, and what do we still need to know? *J Physiol* 2008; 586: 25-34

97. Lexell J. Evidence for nervous system degeneration with advancing age. *J Nutr* 1997; 127: 1011S-1013S

98. Libby P, Ridker PM, and Maseri A. Inflammation and atherosclerosis. *Circulation* 2002; 105: 1135-1143

99. Linke A, Schoene N, Gielen S, Hofer J, Erbs S, Schuler G, and Hambrecht R. Endothelial dysfunction in patients with chronic heart failure: Systemic effects of lower-limb exercise training. *J Am Coll Cardiol* 2001; 37: 392-397

100. Lipkin DP, Jones DA, Round JM, and Poole-Wilson PA. Abnormalities of skeletal muscle in patients with chronic heart failure. *Int J Cardiol* 1988; 18: 187-195

101. Mark DB and Lauer MS. Exercise capacity: The prognostic variable that doesn't get enough respect. *Circulation* 2003; 108: 1534-1536

102. McArdle WD KF, Katch VL. *Exercise physiology. Energy, nutrition, and human performance* Lippincott Williams & Wilkins Philadelphia 2001

103. McCartney N, McKelvie RS, Haslam DR, and Jones NL. Usefulness of weightlifting training in improving strength and maximal power output in coronary artery disease. *Am J Cardiol* 1991; 67: 939-945

104. McCartney N, McKelvie RS, Martin J, Sale DG, and MacDougall JD. Weight-training-induced attenuation of the circulatory response of older males to weight lifting. *J Appl Physiol* 1993; 74: 1056-1060

105. McGuire DK, Levine BD, Williamson JW, Snell PG, Blomqvist CG, Saltin B, and Mitchell JH. A 30-year follow-up of the dallas bedrest and training study: I. Effect of age on the cardiovascular response to exercise. *Circulation* 2001; 104: 1350-1357

106. McKelvie RS. Exercise training in patients with heart failure: Clinical outcomes, safety, and indications. *Heart Fail Rev* 2008; 13: 3-11

107. McKelvie RS, McCartney N, Tomlinson C, Bauer R, and MacDougall JD. Comparison of hemodynamic responses to cycling and resistance exercise in congestive heart failure secondary to ischemic cardiomyopathy. *Am J Cardiol* 1995; 76: 977-979

108. McKelvie RS, Teo KK, McCartney N, Humen D, Montague T, and Yusuf S. Effects of exercise training in patients with congestive heart failure: A critical review. *J Am Coll Cardiol* 1995; 25: 789-796

109. McKelvie RS, Teo KK, Roberts R, McCartney N, Humen D, Montague T, Hendrican K, and Yusuf S. Effects of exercise training in patients with heart failure: The exercise rehabilitation trial (exert). *Am Heart J* 2002; 144: 23-30

110. Mian OS, Thom JM, Ardigo LP, Morse CI, Narici MV, and Minetti AE. Effect of a 12-month physical conditioning programme on the metabolic cost of walking in healthy older adults. *Eur J Appl Physiol* 2007; 100: 499-505

111. Miyamura M and Honda Y. Oxygen intake and cardiac output during maximal treadmill and bicycle exercise. *J Appl Physiol* 1972; 32: 185-188

112. Moore DP, Weston AR, Hughes JM, Oakley CM, and Cleland JG. Effects of increased inspired oxygen concentrations on exercise performance in chronic heart failure. *Lancet* 1992; 339: 850-853

113. Mora S, Redberg RF, Cui Y, Whiteman MK, Flaws JA, Sharrett AR, and Blumenthal RS. Ability of exercise testing to predict cardiovascular and all-cause death in asymptomatic women: A 20-year follow-up of the lipid research clinics prevalence study. *Jama* 2003; 290: 1600-1607

114. Morris JN, Clayton DG, Everitt MG, Semmence AM, and Burgess EH. Exercise in leisure time: Coronary attack and death rates. *Br Heart J* 1990; 63: 325-334

115. Myers J. Cardiology patient pages. Exercise and cardiovascular health. *Circulation* 2003; 107: e2-5

116. Myers J, Kaykha A, George S, Abella J, Zaheer N, Lear S, Yamazaki T, and Froelicher V. Fitness versus physical activity patterns in predicting mortality in men. *Am J Med* 2004; 117: 912-918

117. Myers J, Prakash M, Froelicher V, Do D, Partington S, and Atwood JE. Exercise capacity and mortality among men referred for exercise testing. *N Engl J Med* 2002; 346: 793-801

118. Nagashima K, Mack GW, Haskell A, Nishiyasu T, and Nadel ER. Mechanism for the posture-specific plasma volume increase after a single intense exercise protocol. *J Appl Physiol* 1999; 86: 867-873

119. Narici MV, Maganaris CN, Reeves ND, and Capodaglio P. Effect of aging on human muscle architecture. *J Appl Physiol* 2003; 95: 2229-2234

120. Neill WA, Branch LG, De Jong G, Smith NE, Hogan CA, Corcoran PJ, Jette AM, Balasco EM, and Osberg S. Cardiac disability. The impact of coronary heart disease on patients' daily activities. *Arch Intern Med* 1985; 145: 1642-1647

121. Niebauer J, Hambrecht R, Marburger C, Hauer K, Velich T, von Hodenberg E, Schlierf G, Kubler W, and Schuler G. Impact of intensive physical exercise and low-fat diet on collateral vessel formation in stable angina pectoris and angiographically confirmed coronary artery disease. *Am J Cardiol* 1995; 76: 771-775

122. Nielsen MH and Nielsen NC. Spectrophotometric determination of evans blue dye in plasma with individual correction for blank density by a modified gaeblers method. *Scand J Clin Lab Invest* 1962; 14: 605-617

123. Oberman A, Fletcher GF, Lee J, Nanda N, Fletcher BJ, Jensen B, and Caldwell ES. Efficacy of high-intensity exercise training on left ventricular ejection fraction in men with coronary artery disease (the training level comparison study). *Am J Cardiol* 1995; 76: 643-647

124. Ornish D, Scherwitz LW, Billings JH, Brown SE, Gould KL, Merritt TA, Sparler S, Armstrong WT, Ports TA, Kirkeeide RL, Hogeboom C, and Brand RJ. Intensive lifestyle changes for reversal of coronary heart disease. *Jama* 1998; 280: 2001-2007

125. Osteras H, Helgerud J, and Hoff J. Maximal strength-training effects on force-velocity and force-power relationships explain increases in aerobic performance in humans. *Eur J Appl Physiol* 2002; 88: 255-263

126. Overend TJ, Paterson DH, and Cunningham DA. The effect of interval and continuous training on the aerobic parameters. *Can J Sport Sci* 1992; 17: 129-134

127. Paffenbarger RS, Jr., Blair SN, and Lee IM. A history of physical activity, cardiovascular health and longevity: The scientific contributions of jeremy n morris, dsc, dph, frcp. *Int J Epidemiol* 2001; 30: 1184-1192

128. Paffenbarger RS, Jr., Hyde RT, Wing AL, and Hsieh CC. Physical activity, all-cause mortality, and longevity of college alumni. *N Engl J Med* 1986; 314: 605-613

129. Pate RR and Kriska A. Physiological basis of the sex difference in cardiorespiratory endurance. *Sports Med* 1984; 1: 87-98

130. Peltonen JE, Rantamaki J, Niittymaki SP, Sweins K, Viitasalo JT, and Rusko HK. Effects of oxygen fraction in inspired air on rowing performance. *Med Sci Sports Exerc* 1995; 27: 573-579

131. Peltonen JE, Tikkanen HO, Ritola JJ, Ahotupa M, and Rusko HK. Oxygen uptake response during maximal cycling in hyperoxia, normoxia and hypoxia. *Aviat Space Environ Med* 2001; 72: 904-911

132. Peltonen JE, Tikkanen HO, and Rusko HK. Cardiorespiratory responses to exercise in acute hypoxia, hyperoxia and normoxia. *Eur J Appl Physiol* 2001; 85: 82-88

133. Perrault H. Efficiency of movement in health and chronic disease. *Clin Invest Med* 2006; 29: 117-121

134. Perry CG, Reid J, Perry W, and Wilson BA. Effects of hyperoxic training on performance and cardiorespiratory response to exercise. *Med Sci Sports Exerc* 2005; 37: 1175-1179

135. Piepoli MF, Corra U, Agostoni PG, Belardinelli R, Cohen-Solal A, Hambrecht R, and Vanhees L. Statement on cardiopulmonary exercise testing in chronic heart failure due to left ventricular dysfunction: Recommendations for performance and interpretation part ii: How to perform cardiopulmonary exercise testing in chronic heart failure. *Eur J Cardiovasc Prev Rehabil* 2006; 13: 300-311

136. Piepoli MF, Corra U, Agostoni PG, Belardinelli R, Cohen-Solal A, Hambrecht R, and Vanhees L. Statement on cardiopulmonary exercise testing in chronic heart failure due to left ventricular dysfunction: Recommendations for performance and interpretation. Part i: Definition of cardiopulmonary exercise testing parameters for appropriate use in chronic heart failure. *Eur J Cardiovasc Prev Rehabil* 2006; 13: 150-164

137. Piepoli MF, Davos C, Francis DP, and Coats AJ. Exercise training meta-analysis of trials in patients with chronic heart failure (extramatch). *Bmj* 2004; 328: 189

138. Pinsky JL, Jette AM, Branch LG, Kannel WB, and Feinleib M. The framingham disability study: Relationship of various coronary heart disease manifestations to disability in older persons living in the community. *Am J Public Health* 1990; 80: 1363-1367

139. Plet J, Pedersen PK, Jensen FB, and Hansen JK. Increased working capacity with hyperoxia in humans. *Eur J Appl Physiol Occup Physiol* 1992; 65: 171-177

140. Ploutz-Snyder LL, Simoneau JA, Gilders RM, Staron RS, and Hagerman FC. Cardiorespiratory and metabolic adaptations to hyperoxic training. *Eur J Appl Physiol Occup Physiol* 1996; 73: 38-48

141. Pollock ML. Submaximal and maximal working capacity of elite distance runners. Part i: Cardiorespiratory aspects. *Ann N Y Acad Sci* 1977; 301: 310-322

142. Pons ER, Jr. and Berg JL. The physiologic advantage of oxygen during exercise in patients with coronary artery insufficiency. *Dis Chest* 1961; 39: 551-556

143. Porter MM, Vandervoort AA, and Lexell J. Aging of human muscle: Structure, function and adaptability. *Scand J Med Sci Sports* 1995; 5: 129-142

144. Powell KE, Thompson PD, Caspersen CJ, and Kendrick JS. Physical activity and the incidence of coronary heart disease. *Annu Rev Public Health* 1987; 8: 253-287

145. Powers SK, Lawler J, Dempsey JA, Dodd S, and Landry G. Effects of incomplete pulmonary gas exchange on vo2 max. *J Appl Physiol* 1989; 66: 2491-2495

146. Restrick LJ, Davies SW, Noone L, and Wedzicha JA. Ambulatory oxygen in chronic heart failure. *Lancet* 1992; 340: 1192-1193

147. Richardson RS. What governs skeletal muscle vo2max? New evidence. *Med Sci Sports Exerc* 2000; 32: 100-107

148. Richardson RS, Grassi B, Gavin TP, Haseler LJ, Tagore K, Roca J, and Wagner PD. Evidence of o2 supply-dependent vo2 max in the exercise-trained human quadriceps. *J Appl Physiol* 1999; 86: 1048-1053

149. Richardson RS, Leigh JS, Wagner PD, and Noyszewski EA. Cellular po2 as a determinant of maximal mitochondrial o(2) consumption in trained human skeletal muscle. *J Appl Physiol* 1999; 87: 325-331

150. Riseman JEF and Morton GB. The effect of oxygen on the exercise tolerance of patients with angina pectoris *American Heart Journal* 1939
18: 150-152

151. Robinson S. Experimental studies of physical fintess in relation to age. *Arbeitsphysiology* 1938; 10: 251-323

152. Rogers MA, Hagberg JM, Martin WH, 3rd, Ehsani AA, and Holloszy JO. Decline in vo2max with aging in master athletes and sedentary men. *J Appl Physiol* 1990; 68: 2195-2199

153. Rognmo O, Hetland E, Helgerud J, Hoff J, and Slordahl SA. High intensity aerobic interval exercise is superior to moderate intensity exercise for increasing aerobic capacity in patients with coronary artery disease. *Eur J Cardiovasc Prev Rehabil* 2004; 11: 216-222

154. Russell SD, Koshkarian GM, Medinger AE, Carson PE, and Higginbotham MB. Lack of effect of increased inspired oxygen concentrations on maximal exercise capacity or ventilation in stable heart failure. *Am J Cardiol* 1999; 84: 1412-1416

155. Saltin B. Hemodynamic adaptations to exercise. *Am J Cardiol* 1985; 55: 42D-47D

156. Saltin B and Astrand PO. Maximal oxygen uptake in athletes. *J Appl Physiol* 1967; 23: 353-358

157. Saltin B and Calbet JA. Point: In health and in a normoxic environment, vo2 max is limited primarily by cardiac output and locomotor muscle blood flow. *J Appl Physiol* 2006; 100: 744-745

158. Savage PD, Lee M, Harvey-Berino J, Brochu M, and Ades PA. Weight reduction in the cardiac rehabilitation setting. *J Cardiopulm Rehabil* 2002; 22: 154-160

159. Scheel KW, Ingram LA, and Wilson JL. Effects of exercise on the coronary and collateral vasculature of beagles with and without coronary occlusion. *Circ Res* 1981; 48: 523-530

160. Schulman SP, Fleg JL, Goldberg AP, Busby-Whitehead J, Hagberg JM, O'Connor FC, Gerstenblith G, Becker LC, Katzel LI, Lakatta LE, and Lakatta EG. Continuum of cardiovascular performance across a broad range of fitness levels in healthy older men. *Circulation* 1996; 94: 359-367

161. Selvanayagam JB, Jerosch-Herold M, Porto I, Sheridan D, Cheng AS, Petersen SE, Searle N, Channon KM, Banning AP, and Neubauer S. Resting myocardial blood flow is impaired in hibernating myocardium: A magnetic resonance study of quantitative perfusion assessment. *Circulation* 2005; 112: 3289-3296

162. Shephard RJ and Balady GJ. Exercise as cardiovascular therapy. *Circulation* 1999; 99: 963-972

163. Siscovick DS, Weiss NS, Fletcher RH, and Lasky T. The incidence of primary cardiac arrest during vigorous exercise. *N Engl J Med* 1984; 311: 874-877

164. Smart N, Fang ZY, and Marwick TH. A practical guide to exercise training for heart failure patients. *J Card Fail* 2003; 9: 49-58

165. Spuentrup E and Botnar RM. Coronary magnetic resonance imaging: Visualization of the vessel lumen and the vessel wall and molecular imaging of arteriothrombosis. *Eur Radiol* 2006; 16: 1-14

166. Stathokostas L, Jacob-Johnson S, Petrella RJ, and Paterson DH. Longitudinal changes in aerobic power in older men and women. *J Appl Physiol* 2004; 97: 781-789

167. Sternfeld B, Ngo L, Satariano WA, and Tager IB. Associations of body composition with physical performance and self-reported functional limitation in elderly men and women. *Am J Epidemiol* 2002; 156: 110-121

168. Stevenson ET, Davy KP, and Seals DR. Maximal aerobic capacity and total blood volume in highly trained middle-aged and older female endurance athletes. *J Appl Physiol* 1994; 77: 1691-1696

169. Stuber M, Botnar RM, Danias PG, McConnell MV, Kissinger KV, Yucel EK, and Manning WJ. Contrast agent-enhanced, free-breathing, three-dimensional coronary magnetic resonance angiography. *J Magn Reson Imaging* 1999; 10: 790-799

170. Suetta C, Aagaard P, Magnusson SP, Andersen LL, Sipila S, Rosted A, Jakobsen AK, Duus B, and Kjaer M. Muscle size, neuromuscular activation, and rapid force characteristics in elderly men and women: Effects of unilateral long-term disuse due to hip-osteoarthritis. 2007; 102: 942-948

171. Suetta C, Aagaard P, Rosted A, Jakobsen AK, Duus B, Kjaer M, and Magnusson SP. Training-induced changes in muscle csa, muscle strength, emg, and rate of force development in elderly subjects after long-term unilateral disuse. 2004; 97: 1954-1961

172. Svartberg J, von Muhlen D, Mathiesen E, Joakimsen O, Bonaa KH, and Stensland-Bugge E. Low testosterone levels are associated with carotid atherosclerosis in men. *J Intern Med* 2006; 259: 576-582

173. Tanaka H and Seals DR. Endurance exercise performance in masters athletes: Age-associated changes and underlying physiological mechanisms. *J Physiol* 2008; 586: 55-63

174. Thomas TR, Adeniran SB, and Etheridge GL. Effects of different running programs on vo2 max, percent fat, and plasma lipids. *Can J Appl Sport Sci* 1984; 9: 55-62

175. Thompson PD, Buchner D, Pina IL, Balady GJ, Williams MA, Marcus BH, Berra K, Blair SN, Costa F, Franklin B, Fletcher GF, Gordon NF, Pate RR, Rodriguez BL, Yancey AK, and Wenger NK. Exercise and physical activity in the prevention and treatment of atherosclerotic cardiovascular disease: A statement from the council on clinical cardiology (subcommittee on exercise, rehabilitation, and prevention) and the council on nutrition, physical activity, and metabolism (subcommittee on physical activity). *Circulation* 2003; 107: 3109-3116

176. Thompson PD, Franklin BA, Balady GJ, Blair SN, Corrado D, Estes NA, 3rd, Fulton JE, Gordon NF, Haskell WL, Link MS, Maron BJ, Mittleman MA, Pelliccia A, Wenger NK, Willich SN, and Costa F. Exercise and acute cardiovascular events placing the risks into perspective: A scientific statement from the american heart association council on nutrition, physical activity, and metabolism and the council on clinical cardiology. *Circulation* 2007; 115: 2358-2368

177. van Tol BA, Huijsmans RJ, Kroon DW, Schothorst M, and Kwakkel G. Effects of exercise training on cardiac performance, exercise capacity and quality of life in patients with heart failure: A meta-analysis. *Eur J Heart Fail* 2006; 8: 841-850

178. Vandervoort AA. Aging of the human neuromuscular system. *Muscle Nerve* 2002; 25: 17-25

179. Vandervoort AA and McComas AJ. Contractile changes in opposing muscles of the human ankle joint with aging. *J Appl Physiol* 1986; 61: 361-367

180. Volaklis KA and Tokmakidis SP. Resistance exercise training in patients with heart failure. *Sports Med* 2005; 35: 1085-1103

181. Wagner PD. Gas exchange and peripheral diffusion limitation. *Med Sci Sports Exerc* 1992; 24: 54-58

182. Wagner PD. New ideas on limitations to vo2max. *Exerc Sport Sci Rev* 2000; 28: 10-14

183. Warburton DE, Haykowsky MJ, Quinney HA, Blackmore D, Teo KK, Taylor DA, McGavock J, and Humen DP. Blood volume expansion and cardiorespiratory function: Effects of training modality. *Med Sci Sports Exerc* 2004; 36: 991-1000

184. Warburton DE, McKenzie DC, Haykowsky MJ, Taylor A, Shoemaker P, Ignaszewski AP, and Chan SY. Effectiveness of high-intensity interval training for the rehabilitation of patients with coronary artery disease. *Am J Cardiol* 2005; 95: 1080-1084

185. Welch HG. Hyperoxia and human performance: A brief review. *Med Sci Sports Exerc* 1982; 14: 253-262

186. Wenger HA and Bell GJ. The interactions of intensity, frequency and duration of exercise training in altering cardiorespiratory fitness. *Sports Med* 1986; 3: 346-356

187. White FC, Bloor CM, McKirnan MD, and Carroll SM. Exercise training in swine promotes growth of arteriolar bed and capillary angiogenesis in heart. *J Appl Physiol* 1998; 85: 1160-1168

188. Widlansky ME, Gokce N, Keaney JF, Jr., and Vita JA. The clinical implications of endothelial dysfunction. *J Am Coll Cardiol* 2003; 42: 1149-1160

189. Wielenga RP, Coats AJ, Mosterd WL, and Huisveld IA. The role of exercise training in chronic heart failure. *Heart* 1997; 78: 431-436

190. Wielenga RP, Erdman RA, Huisveld IA, Bol E, Dunselman PH, Baselier MR, and Mosterd WL. Effect of exercise training on quality of life in patients with chronic heart failure. *J Psychosom Res* 1998; 45: 459-464

191. Wilson TM and Tanaka H. Meta-analysis of the age-associated decline in maximal aerobic capacity in men: Relation to training status. *Am J Physiol Heart Circ Physiol* 2000; 278: H829-834

192. Wisloff U, Helgerud J, Stoylen A, and Ellingsen O. Atrioventricular plane displacement in female endurance athletes. *Med Sci Sports Exerc* 2001; 33: 1503-1510

193. Wisloff U, Stoylen A, Loennechen JP, Bruvold M, Rognmo O, Haram PM, Tjonna AE, Helgerud J, Slordahl SA, Lee SJ, Videm V, Bye A, Smith GL, Najjar SM, Ellingsen O, and Skjaerpe T. Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients: A randomized study. *Circulation* 2007; 115: 3086-3094

194. Yoshinaga K, Beanlands RS, Dekemp RA, Lortie M, Morin J, Aung M, McKelvie R, and Davies RF. Effect of exercise training on myocardial blood flow in patients with stable coronary artery disease. *Am Heart J* 2006; 151: 1324 e1311-1328

195. You Fang Z and Marwick TH. Mechanisms of exercise training in patients with heart failure. *Am Heart J* 2003; 145: 904-911

196. Zhou B, Conlee RK, Jensen R, Fellingham GW, George JD, and Fisher AG. Stroke volume does not plateau during graded exercise in elite male distance runners. *Med Sci Sports Exerc* 2001; 33: 1849-1854

197. Zipes DP, Libby P, Bonow RO, and Braunwald E. *Braunwald's heart disease. A textbook of cardiovascular medicine* Elsevier Saunders, Philadelphia, 2005

198. Aagaard P, Simonsen EB, Andersen JL, Magnusson P, and Dyhre-Poulsen P. Neural adaptation to resistance training: Changes in evoked v-wave and h-reflex responses. *J Appl Physiol* 2002; 92: 2309-2318

199. Åstrand K, Rodahl PO, Dahl HA, and Strømme SB. *Textbook of work physiology. Physiological bases of exercise* Human Kinetics Leeds 2003

200. Åstrand PO and Rodahl K. *Textbook of work physiology. Physiological bases of exercise* McGraw-Hill Book Company New York 1986

PAPER I

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PAPER III

Aerobic interval training improves VO_{2peak} in coronary artery disease patients; no additional effect from hyperoxia

Hyperoxic aerobic interval training

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Abstract

Objectives. To investigate whether hyperoxic aerobic interval training improves training quality in coronary artery disease patients. **Design.** Twenty-one stable coronary artery disease patients were recruited to hyperoxic (n=10) and normoxic (n=11) groups (age: 62.4 ± 6.8 years). Patients underwent 30 supervised 4x4 minutes interval training sessions using treadmill walking, at 85-95% of peak heart rate. **Results.** Arterial saturation was significantly increased by 3% at pretest from normoxic to hyperoxic testing conditions. Peak oxygen uptake and stroke volume increased significantly by 16% and 17% ($p < 0.05$) and by 16 % and 18 % ($p < 0.05$) in the hyperoxic and normoxic training groups respectively. No difference was revealed between groups for peak oxygen uptake and stroke volume. Blood volumes were unchanged from pre to post training. Peak oxygen uptake measured in normoxia and hyperoxia in the hyperoxia training group revealed no difference. **Conclusion.** The present study shows that breathing 100% oxygen enriched air during aerobic interval training in stable coronary artery disease patients does not improve peak oxygen uptake above the level attained with normoxic training.

Keywords

100% oxygen; Endurance training; 4x4 minutes intervals; maximal oxygen uptake; Stroke volume

Introduction

Endurance training is an effective means in prevention and rehabilitation of coronary artery disease and VO_{2max} identified as the single best predictor of mortality [8]. Our research group has previously shown that in short term interventions high intensity aerobic interval training is superior to moderate intensity training for increasing aerobic power in coronary artery disease (CAD) patients [18]. Reduced stroke volume has been reported at rest and maximal exercise in coronary artery disease patients in whom exercise induced myocardial ischemia may reduce the myocardial contractile function [20]. Improvements in VO_{2max} after aerobic interval training has been linked to improved maximal stroke volume [5]. Increased left ventricular ejection fraction and remodeling of the left ventricle associated with increased VO_{2max} have been noted in heart failure patients after interval training [24]. A few training studies have investigated the effect of hyperoxic training on healthy subjects, showing a 8-9 % increase in exercise load at the same heart rate during hyperoxic training, but none have found significant effect on VO_{2max} after 5- and 6 weeks of hyperoxic endurance training [11, 13]. These finding are in contrast to the well documented increase seen in VO_{2max} and performance during acute inspiration of hyperoxic gas [10, 12, 16]. In CAD patients oxygen breathing increased the angina threshold allowing the heart to do more work before the development of coronary insufficiency [6], and increased exercise performance [6, 7, 14, 17]. Some studies recommend use of oxygen during physical activity, especially to patients with anginal pain and ischemic ST depression after exercise. Aerobic interval training in hyperoxia may increase the exercise power output from normoxic training without raising the already high training heart rate, with the potential of increasing the training outcome [11, 13]. Both duration and intensity of the training intervention in hyperoxia are crucial. No hyperoxic training study has to our knowledge been performed with CAD patients, who may have reduced ability for oxygen delivery to the working muscles through reduced myocardial contractility and stroke volume if ischemic [20]. If hyperoxia increases the training work load at the normoxic training heart rate, it might increase the training quality, improving stroke volume and VO_{2peak} to a greater extent than normoxic exercise. The purpose of this study was to investigate whether breathing 100% oxygen enriched air during aerobic interval training in cardiovascular disease patients improves the training outcome compared to aerobic interval training in normoxic conditions.

Methods

Twenty-one clinically diagnosed stable coronary artery disease (CAD) patients were recruited and randomly allocated to a hyperoxic training group (HT) n = 10, and a normoxic training group (NT) n = 11 from the St. Olav University Hospital of Trondheim. Physical descriptions of patients are shown in table 1. Inclusion criteria were stable CAD, angina pectoris class I-III in the Canadian Cardiovascular Society Classification (CCS), ischemia in exercise electrocardiogram, or angiographically documented cardiovascular disease. Exclusion criteria were unstable angina pectoris, myocardial infarction during the last month, percutaneous coronary intervention (PCI) during the last month, left ventricular ejection fraction below 40%, complex ventricular arrhythmias, and orthopedic or neurological limitations to exercise. The following number of patients used the listed medication; beta-blockers (13), antiplatelet agents (15), statins (13), angiotensin-converting-enzyme inhibitors (3), long-acting nitrates (2), and diuretics (2). No change in medication was reported during the study.

The study protocol was approved by the regional committee for medical research ethics, and was accomplished according to the declaration of Helsinki. Written consent was obtained from the subjects. Two patients dropped out of the study while 1 patient was excluded due to repeated non- cardiac illness affecting training quality.

Exercise testing were performed pre and post the exercise training period. VO_{2peak} were tested in both normoxia (21% oxygen) and hyperoxia (65% oxygen) in the HT in a random order 2 days apart while VO_{2peak} were tested in normoxia (21% oxygen) in the NT. Respiratory testing (V-max Spectra, SensorMedics, USA) were performed during treadmill walking at 3-5 km per hour (Technogym, Italy). The treadmill inclination was raised (1-3%/min) until subjects reached exhaustion, and the average of the three continuous highest 10 seconds measurements determined VO_{2peak}. Criteria for exhaustion were an RQ value above 1.0 and a Borg scale value above 15. RQ was above 1.0 in all patients and Borg scale values above 15 were observed in 14 patients. In addition, the authors did a subjective evaluation of the level of exhaustion through observations of ventilation, walking action and facial expressions in patients at the end stage of the test.

Heart rate (HR) was measured by a heart rate monitor (Polar Sport, Finland), while arterial oxygen saturation (SpO_2) was recorded by pulsoximetry in the HT (Critcare Systems INC, USA). A capillary blood sample taken immediately after the tests, was analyzed for lactate using an YSI 1500 sport tester (YSI Incorporated, USA). Patients self reported exercise exertion through the 6-20 Borg scale for ratings of perceived exertion [1].Cardiac output (CO) was measured during treadmill walking at 80% of VO_{2peak} through acetylene breathing according to the methods previously described by Helgerud et al [5]. During steady state walking patients did one complete inspiration and expiration of acetylene gas mixture where inspiration and expiration values of gases were used to calculate cardiac output. The test method has previously been validated and a coefficient of variation of 7.6% was found [3]. Blood- and plasma volume was measured before and after training in the HT using the Evans blue dye dilution technique [9], according to procedures previously described [5]. The questionnaires SF36 and Macnew were distributed to the patients for measurements of quality of life before and after the training periods.

Interval Training

Patients completed 30 interval sessions with treadmill walking in three weekly sessions during 10 weeks after the initial testing. Subjects in the hyperoxic and the normoxic training group had a compliance of respectively 29.6 ± 0.7 and 29.1 ± 1.1 training sessions. 100% oxygen enriched air was distributed to the patients in the HT during exercise. Gas was distributed to the patients from a Douglas bag connected to a gas tank, and patient breathed through a face mask and a three way valve system. No discomfort was noted due to training with a facial mask, and consequently all subjects were able to adhere properly to the training intensity. After 5 minutes warm up, patients continued with 4 times 4 minutes of interval training, with 3 minutes active breaks in-between each interval. During the 4 minutes intervals patients trained at 85-95% of HR_{peak}, while during active breaks intensity was at 60-70% of HR_{peak}. To compensate for increased VO_{2peak} capacity, treadmill speed and grade were increased several times during the study, to make sure the patients trained at 85-95% of their HR_{peak} at all times. HR and SpO_2 were recorded during exercise and patients reported self reported exercise stamina through the 6-20 Borg scale for ratings of perceived exertion [1].

All training sessions were supervised by an exercise physiologist. Two subjects in each training group experienced angina pain during the start of training sessions early in the study, but were able to continue training without having to use nitroglycerine. No other cardiac related incidents were reported during the study.

All values are expressed as mean ± standard deviation (SD). Changes within groups were determined by the Wilcoxon signed ranks test. Differences between the HT and the NT response to training were calculated by using the Mann-Whitney U-test. A two-tailed $p < 0.05$ was accepted as statistically significant for all tests.

With a power of 0.80 and a two sided α value of 0.05 and an expected difference in training work load of 8% the calculated number of subjects needed in each group was 7.

Results

$VO_{2peak,}$ performance, peak ventilation, peak cardiac output and stroke volume increased significantly from pre to post training in both training groups (figure 1; table 2; table 3) together with scores for physical (10%) and social (9%) quality of life in the HT, and total (9%), physical (13%) and social score (10%) in the NT measured by the Macnew questionnaire. No difference was found between groups in the improvement in VO_{2peak}, performance, peak cardiac output and stroke volume from pre to post the training intervention. Peak oxygen saturation was significantly increased by 3% ($p < 0.05$) from normoxic to hyperoxic testing in the HT (table 2; table 4). VO_{2peak} and performance in the HT was equal in hyperoxic and normoxic testing both before and after training (table 2; table 4). Peak heart rate and lactate increased significantly from pre to post training in the HT, and the HT had a significantly greater increase in peak ventilation than the NT, while the opposite were true for perceived exertion through the Borg scale (table 2). All other measures, including total blood volume were not significantly different (table 5).

The Borg rate of perceived exertion after each training session was 16.3 ± 0.7 for the HT, and 14.4 ± 1 for the NT. One patient in the HT showed an elevated exercise ST segment after the training period and was referred for further examination at the cardiac unit at the University hospital.

Discussion

The most important finding in this experiment was that stable coronary artery disease patients breathing 100% oxygen enriched air during interval training did not show a superior training effect over patients training in normoxic conditions. Although arterial oxygen saturation was significantly improved in the hyperoxic pretest compared to the normoxic pretest in the hyperoxic training group, hyperoxic training showed no additional effect on peak VO_2, performance, cardiac output or stroke volume compared to normoxic training. In addition no acute effect of hyperoxia was detected on VO_{2peak} in the hyperoxic training group before or after the training period.

Hyperoxic breathing in cardiovascular disease patients may improve oxygen delivery to the myocardium and the skeletal muscles. The use of hyperoxic gas has been found to restore electrocardiographic abnormalities in cardiovascular disease patients [14], and may protect the myocardium from the hypoxic effect of exercise and increase the angina threshold [6]. The negative effect of ischemia with reduced myocardial contractility and stroke volume during high intensity training may thereby be prevented. In the present study, a 3% increase in arterial oxygen saturation may not be sufficient to overcome a potential ischemic exercise restriction during interval exercise, or an oxygen desaturation of 95% may not have been low enough to cause myocardial insufficiencies in normoxia effecting aerobic performance. A significant increase in SpO_2 from 95% to 98% has been reported to be sufficient to increase exercise performance in chronic heart failure patients [7], so our patients may be at borderline in terms of getting effect from oxygen supplementation on hemoglobin oxygen saturation and training load. In addition the present study may not have succeeded in recruiting a severe enough ischemic patient population to gain effect from increased myocardial oxygen delivery. Due to treatment options like PCI and coronary bypass surgery fewer severe angina patients seems to be available as volunteers, and the level of angina might be milder. Hyperoxic supplementation permits the ischemic heart to carry out more work before coronary insufficiency develop [6] and may therefore be effective in a severe ischemic patient group with greater limitation in cardiovascular function during peak exercise.

A great number of studies have found VO_{2max} and performance increased in acute hyperoxia, alongside an increased hemoglobin oxygen saturation and arterial oxygen content [6, 10, 12, 14, 16, 17], however all data do not point in the same direction in terms of heart patients. When studying the acute effect of hyperoxia in coronary artery disease patients, some investigations did not detect improvements in VO_{2peak} and performance. In one investigation, haemoglobin oxygen saturation was not increased in hyperoxia compared to normoxia, however, a trend of reduction in leg blood flow was detected implying that hyperoxia did not improve muscle oxygen delivery, thereby explaining the lack of effect on leg oxygen uptake and performance [19]. In another study of heart failure patients haemoglobin oxygen saturation was increased in hyperoxia however no improvements in VO_{2max} and performance was noted [15]. The present study displays similar results with equal VO_{2peak} in hyperoxia and normoxia both before and after the hyperoxic training intervention. The lack of improvement in VO_{2peak} in hyperoxia may be a result of decreased leg blood flow. In a study by Russell and colleagues [19], a trend towards reduced leg blood flow was observed despite of no change in haemoglobin oxygen saturation. In the present study, in which SpO_2 was significantly increased during hyperoxic testing, one might suggest that leg blood flow may significantly be reduced resulting in no additional oxygen delivery to the working skeletal muscles serving as an explanation for absence of additional oxygen consumption in hyperoxia and the lack of effect from hyperoxic training. This could explain the deficiency of accumulative effect of hyperoxia on VO_{2peak} and stroke volume over time with aerobic interval training despite increased haemoglobin oxygen saturation and the theoretical possibility of increased oxygen delivery to the working muscles.

Increased training work load has been reported during hyperoxic training in previous studies [11, 13]. In those training studies in healthy subjects hyperoxic exposure enabled the subjects to increase the training work load by 8-9% at the normoxic training heart rate. Despite increased training work load hyperoxic training was not found to be superior in terms of VO_{2max} and performance enhancement [11, 13]. This is in line with the present study where no difference was found between the effects of interval training in hyperoxia and normoxia. In the study by Ploutz-Snyder et al [13] the lack of improvement in VO_{2max} after hyperoxic training may be explained by the relatively low training intensity (70% of maximal heart rate), while intensity levels above 85% of peak heart rate was used by Perry et al [11] and in the present study, and

thereby should be optimal for detecting any effects of hyperoxic training on stroke volume and VO_{2peak} [18, 24].

The notion in this experiment was that the ability of CAD patients` muscles to increase the a-vO_2 difference as shown in a study of intermittent claudication patients [21] would enable the patients to utilize the extra 3% arterial oxygen saturation during training leading to a cumulative positive effect on both workload and training response during the 30 interval sessions. As this did not happen, other explanations may be that the a-vO_2 difference did not change fast enough to pick up the advantage of extra oxygen. However, great changes in a-vO_2 difference has been shown in previous experiments [16] and may not be the most likely cause. The most probable reason for the lack of improved training effect from a higher arterial oxygen saturation is that hyperoxic exercise, despite higher blood oxygen carrying capacity, does not increase the exercise induced load on the heart compared to normoxic training conditions. Thereby the main limiting factor for VO_{2peak}, namely, the stroke volume of the heart changed to the same degree in the two training groups. One may speculate that the improvement in stroke volume in the two groups improves the blood and oxygen supply to the working muscles to a similar extent as the improvement in the muscles ability to utilize oxygen since no additional affect of hyperoxia was detected at post testing. Since the difference between normoxic and hyperoxic training is arterial oxygen content and not cardiac output or shear stress in the blood supply chain, these findings seem to support Wagner's [22] notion that the oxygen supply is of the greater importance than the demand for oxygen in terms of explaining training induced changes.

Despite the lack of difference in the training response between normoxic and hyperoxic training, a substantial improvement in VO_{2peak} following 30 interval sessions using 4x4 minutes interval training at 85 to 95 % of maximal heart rate was found. The 16–17% improvement in VO_{2peak} confirms that aerobic interval training at 85-95% of HR_{peak} is highly effective for improving VO_{2peak} and stroke volume in coronary artery disease patients [4, 18].

No significant change in total blood-or plasma volume was observed from pre to post training in the HT in the present study (table 5). Red blood cell mass was, however, significantly decreased after exercise. The findings in the present study differ from the data of the studies reporting long

term changes in plasma volume with aerobic exercise [23], but in line with others having found no change [2, 5]. A reduced red cell mass could decrease the oxygen carrying capacity of the blood, and thereby could not explain the improved VO_{2peak} in this experiment.

In the present study the HT group displayed a significant improvement in peak heart rate and lactate concentration from pre to post training. Both the HT and the NT training groups improved peak ventilation from pre to post training as expected from improvements in VO_{2peak}. The HT group did however improve ventilation to a greater extent than the NT group. Improvements in these variables in the HT group may be a result of a greater motivation to push through to exhaustion during VO_{2peak} post testing. Part of the increased heart rate may be due to atria fibrillation during exercise, and not a true difference in exertion during pre and post testing. In the NT group significant increase in self reported perceived exertion from pre to post training may be a factor of patients adjusting their perception of exercise strain over the course of the training intervention. Despite differences between the groups at the pretesting point in the Borg scale, no significant difference in R values was noted between the groups or in any of the exercise groups between the pre and the post tests. This implies that the level of strain and hyperventilation was equal between the tests. Therefore, change in the perceived exertion was not an effect of greater level of exhaustion in the post test, but a factor of the patients' interpretation of the scale.

In the present study breathing 100% oxygen enriched air during high intensity aerobic interval training improves VO_{2peak} to the same extent as ambient air training in stable coronary artery disease patients with mild to moderate coronary ischemic response to exercise.

Table 1 Physical characteristic of the subjects at inclusion

	Hyperoxic training group (n=8)	Normoxic training group (n=10)
Men/women	6/2	7/3
Age (years)	61.1 ± 7.1	63.6 ± 6.5
Stature (cm)	175.5 ± 11.1	173.4 ± 9.2
Body mass (kg)	82.3 ± 13.2	79.3 ± 12.2
Body mass index ($kg \cdot m^{-2}$)	27.2 ± 2.8	26.3 ± 2.6
Systolic blood pressure (mmHg)	130 ± 27	139 ± 20
Diastolic blood pressure (mmHg)	77 ± 10	84 ± 8
Coronary artery disease		
Myocardial infarction	1	3
Percutaneous coronary intervention	4	4
Coronary artery bypass surgery	5	3

Table 2 Peak metabolic data in normoxia before and after training

	Hyperoxic training group (n=8)		Normoxic training group (n=10)	
	Before	After	Before	After
Oxygen uptake				
$L \cdot min^{-1}$	2.11 ± 0.35	2.44 ± 0.48 *	2.17 ± 0.53	2.53 ± 0.61*
$mL \cdot kg^{-1} \cdot min^{-1}$	25.9 ± 4.2	29.9 ± 3.9 *	27.3 ± 4.6	31.8 ± 5.0*
$mL \cdot kg^{-0.75} \cdot min^{-1}$	77.7 ± 11.3	89.6 ± 11.6 *	81.4 ± 14.4	94.8 ± 16.1*
Heart rate ($beats \cdot min^{-1}$)	141 ± 19	152 ± 19 *	163 ± 19	160 ± 19
Ventilation (BTPS) ($L \cdot min^{-1}$)	72.6 ± 14.4	87.3 ± 19.2 *#	86.1 ± 19.8	92.7 ± 24.2*
Respiratory exchange ratio	1.11 ± 0.08	1.20 ± 0.10	1.14 ± 0.06	1.15 ± 0.07
Work load (watt)	123 ± 27	159 ± 37 *	155 ± 38	204 ± 21*
Arterial oxygen saturation (%)	95 ± 3	95 ± 3	-	-
Lactate ($mmol \cdot L^{-1}$)	3.61 ± 1.01	6.90 ± 1.57 *	4.30 ± 1.20	6.23 ± 1.80
Borg scale	18 ± 1**	18 ± 1	15 ± 2	17 ± 1*#

Data are presented as mean ± SD for each variable.

* Significant difference between pre and post tests within exercise groups ($p < 0.05$)

** Significant difference between groups at pre test time point

Significant difference between groups ($p < 0.05$)

Table 3 Peak cardiac function at 80% of VO_{2peak} work load before and after training

		Hyperoxic training group (n=8)		**Normoxic training group (n=10)**	
		Before	After	Before	After
Heart rate	(beat•min^{-1})	112 ± 11	125 ± 14 *	127 ± 19	133 ± 19
Cardiac output	(L•min^{-1})	11.0 ± 2.1	14.1 ± 2.3 *	12.1 ± 2.6	14.9 ± 3.5*
Stroke volume	(mL•beat^{-1})	98.9 ± 18.9	114.2 ± 21.3 *	95.5 ± 20.8	112.2 ± 21.1*

* Significant difference between pre and post tests within exercise groups ($p < 0.05$)

Table 4 Peak metabolic data from hyperoxic testing in the hyperoxic training group (n = 8)

	Before	After
Oxygen uptake		
L•min^{-1}	2.07 ± 0.35	2.41 ± 0.43
mL•kg^{-1}•min^{-1}	25.3 ± 4.0	29.7 ± 4.0
mL•kg$^{-0,75}$•min^{-1}	76.0 ± 11.3	88.9 ± 11.0
Heart rate (beats•min^{-1})	140 ± 21	151 ± 17
Ventilation (BTPS) (L•min^{-1})	55.5 ± 10.4	69.5 ± 10.4
Respiratory exchange ratio	0.96 ± 0.03	1.15 ± 0.14†
Work load (watt)	121.0 ± 34.3	158.7 ± 34.2
Arterial oxygen saturation (%)	98 ± 2	98 ± 3 †
Lactate (mmol•L^{-1})	2.50 ± 1.06	5.71 ± 2.14
Borg scale	18 ± 2	18 ± 2

Data are presented as mean ± SD for each variable.

† Significant differences between normoxic and hyperoxic tests ($p < 0.05$)

Table 5 Blood volume before and after training in the hyperoxic training group (n = 8)

	Before	After
Blood volume (L)	4.28 ± 0.67	4.25 ± 0.71
Plasma volume (L)	2.81 ± 0.36	2.87 ± 0.42
Red cell mass (L)	1.47 ± 0.34	1.39 ± 0.32 *
Blood volume (mL•kg^{-1})	52.29 ± 8.74	52.23 ± 7.60
Plasma volume (mL•kg^{-1})	34.47 ± 5.69	35.21 ± 4.94
Red cell mass (mL•kg^{-1})	17.81 ± 3.69	17.01 ± 3.26 *
Hematocrit (%)	39.1 ± 3.5	37.3 ± 3.1 *

* Significant difference between pre and post tests ($p < 0.05$)

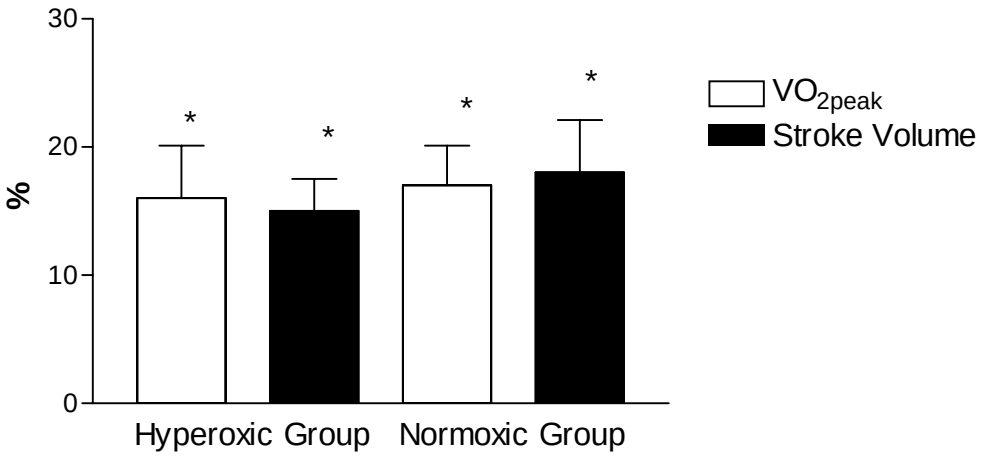

Figure 1.

% change in VO_{2peak} (L • min^{-1}) and peak stroke volume (mL • $stroke^{-1}$) from pre and post training for the hyperoxic and normoxic training groups presented as mean ± SE. Significant difference within groups from pre to post training; * = $p < 0.05$

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References

1. Borg E and Kaijser L. A comparison between three rating scales for perceived exertion and two different work tests. *Scand J Med Sci Sports* 2006; 16: 57-69

2. Branch JD, 3rd, Pate RR, Bourque SP, Convertino VA, Durstine JL, and Ward DS. Exercise training and intensity does not alter vascular volume responses in women. *Aviat Space Environ Med* 1999; 70: 1070-1076

3. Dibski DW, Smith DJ, Jensen R, Norris SR, and Ford GT. Comparison and reliability of two non-invasive acetylene uptake techniques for the measurement of cardiac output. *Eur J Appl Physiol* 2005; 94: 670-680

4. Erbs S, Linke A, Gielen S, Fiehn E, Walther C, Yu J, Adams V, Schuler G, and Hambrecht R. Exercise training in patients with severe chronic heart failure: Impact on left ventricular performance and cardiac size. A retrospective analysis of the leipzig heart failure training trial. *Eur J Cardiovasc Prev Rehabil* 2003; 10: 336-344

5. Helgerud J, Hoydal K, Wang E, Karlsen T, Berg P, Bjerkaas M, Simonsen T, Helgesen C, Hjorth N, Bach R, and Hoff J. Aerobic high-intensity intervals improve vo2max more than moderate training. *Med Sci Sports Exerc* 2007; 39: 665-671

6. Horvat M, Yoshida S, Prakash R, Marcus HS, Swan HJ, and Ganz W. Effect of oxygen breathing on pacing-induced angina pectoris and other manifestations of coronary insufficiency. *Circulation* 1972; 45: 837-844

7. Moore DP, Weston AR, Hughes JM, Oakley CM, and Cleland JG. Effects of increased inspired oxygen concentrations on exercise performance in chronic heart failure. *Lancet* 1992; 339: 850-853

8. Myers J, Prakash M, Froelicher V, Do D, Partington S, and Atwood JE. Exercise capacity and mortality among men referred for exercise testing. *N Engl J Med* 2002; 346: 793-801

9. Nielsen MH and Nielsen NC. Spectrophotometric determination of evans blue dye in plasma with individual correction for blank density by a modified gaeblers method. *Scand J Clin Lab Invest* 1962; 14: 605-617

10. Peltonen JE, Tikkanen HO, Ritola JJ, Ahotupa M, and Rusko HK. Oxygen uptake response during maximal cycling in hyperoxia, normoxia and hypoxia. *Aviat Space Environ Med* 2001; 72: 904-911

11. Perry CG, Reid J, Perry W, and Wilson BA. Effects of hyperoxic training on performance and cardiorespiratory response to exercise. *Med Sci Sports Exerc* 2005; 37: 1175-1179

12. Plet J, Pedersen PK, Jensen FB, and Hansen JK. Increased working capacity with hyperoxia in humans. *Eur J Appl Physiol Occup Physiol* 1992; 65: 171-177

13. Ploutz-Snyder LL, Simoneau JA, Gilders RM, Staron RS, and Hagerman FC. Cardiorespiratory and metabolic adaptations to hyperoxic training. *Eur J Appl Physiol Occup Physiol* 1996; 73: 38-48

14. Pons ER, Jr. and Berg JL. The physiologic advantage of oxygen during exercise in patients with coronary artery insufficiency. *Dis Chest* 1961; 39: 551-556

15. Restrick LJ, Davies SW, Noone L, and Wedzicha JA. Ambulatory oxygen in chronic heart failure. *Lancet* 1992; 340: 1192-1193

16. Richardson RS, Grassi B, Gavin TP, Haseler LJ, Tagore K, Roca J, and Wagner PD. Evidence of o2 supply-dependent vo2 max in the exercise-trained human quadriceps. *J Appl Physiol* 1999; 86: 1048-1053

17. Riseman JEF and Morton GB. The effect of oxygen on the exercise tolerance of patients with angina pectoris *American Heart Journal* 1939
18: 150-152

18. Rognmo O, Hetland E, Helgerud J, Hoff J, and Slordahl SA. High intensity aerobic interval exercise is superior to moderate intensity exercise for increasing aerobic capacity in patients with coronary artery disease. *Eur J Cardiovasc Prev Rehabil* 2004; 11: 216-222

19. Russell SD, Koshkarian GM, Medinger AE, Carson PE, and Higginbotham MB. Lack of effect of increased inspired oxygen concentrations on maximal exercise capacity or ventilation in stable heart failure. *Am J Cardiol* 1999; 84: 1412-1416

20. Selvanayagam JB, Jerosch-Herold M, Porto I, Sheridan D, Cheng AS, Petersen SE, Searle N, Channon KM, Banning AP, and Neubauer S. Resting myocardial blood flow is impaired in hibernating myocardium: A magnetic resonance study of quantitative perfusion assessment. *Circulation* 2005; 112: 3289-3296

21. Slordahl SA, Wang E, Hoff J, Kemi OJ, Amundsen BH, and Helgerud J. Effective training for patients with intermittent claudication. *Scand Cardiovasc J* 2005; 39: 244-249

22. Wagner PD. New ideas on limitations to vo2max. *Exerc Sport Sci Rev* 2000; 28: 10-14

23. Warburton DE, Haykowsky MJ, Quinney HA, Blackmore D, Teo KK, Taylor DA, McGavock J, and Humen DP. Blood volume expansion and cardiorespiratory function: Effects of training modality. *Med Sci Sports Exerc* 2004; 36: 991-1000

24. Wisloff U, Stoylen A, Loennechen JP, Bruvold M, Rognmo O, Haram PM, Tjonna AE, Helgerud J, Slordahl SA, Lee SJ, Videm V, Bye A, Smith GL, Najjar SM, Ellingsen O, and Skjaerpe T. Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients: A randomized study. *Circulation* 2007; 115: 3086-3094

PAPER IV

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34. Terje Skjærpe: NONINVASIVE QUANTITATION OF GLOBAL PARAMETERS ON LEFT VENTRICULAR FUNCTION: THE SYSTOLIC PULMONARY ARTERY PRESSURE AND CARDIAC OUTPUT.
35. Eyvind Rødahl: STUDIES OF IMMUNE COMPLEXES AND RETROVIRUS-LIKE ANTIGENS IN PATIENTS WITH ANKYLOSING SPONDYLITIS.
36. Ketil Thorstensen: STUDIES ON THE MECHANISMS OF CELLULAR UPTAKE OF IRON FROM TRANSFERRIN.
37. Anna Midelfart: STUDIES OF THE MECHANISMS OF ION AND FLUID TRANSPORT IN THE BOVINE CORNEA.
38. Eirik Helseth: GROWTH AND PLASMINOGEN ACTIVATOR ACTIVITY OF HUMAN GLIOMAS AND BRAIN METASTASES - WITH SPECIAL REFERENCE TO TRANSFORMING GROWTH FACTOR BETA AND THE EPIDERMAL GROWTH FACTOR RECEPTOR.
39. Petter C. Borchgrevink: MAGNESIUM AND THE ISCHEMIC HEART.
40. Kjell-Arne Rein: THE EFFECT OF EXTRACORPOREAL CIRCULATION ON SUBCUTANEOUS TRANSCAPILLARY FLUID BALANCE.
41. Arne Kristian Sandvik: RAT GASTRIC HISTAMINE.
42. Carl Bredo Dahl: ANIMAL MODELS IN PSYCHIATRY.

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43. Torbjørn A. Fredriksen: CERVICOGENIC HEADACHE.
44. Rolf A. Walstad: CEFTAZIDIME.
45. Rolf Salvesen: THE PUPIL IN CLUSTER HEADACHE.
46. Nils Petter Jørgensen: DRUG EXPOSURE IN EARLY PREGNANCY.
47. Johan C. Ræder: PREMEDICATION AND GENERAL ANAESTHESIA IN OUTPATIENT GYNECOLOGICAL SURGERY.
48. M. R. Shalaby: IMMUNOREGULATORY PROPERTIES OF TNF-α AND THE RELATED CYTOKINES.
49. Anders Waage: THE COMPLEX PATTERN OF CYTOKINES IN SEPTIC SHOCK.
50. Bjarne Christian Eriksen: ELECTROSTIMULATION OF THE PELVIC FLOOR IN FEMALE URINARY INCONTINENCE.
51. Tore B. Halvorsen: PROGNOSTIC FACTORS IN COLORECTAL CANCER.

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52. Asbjørn Nordby: CELLULAR TOXICITY OF ROENTGEN CONTRAST MEDIA.
53. Kåre E. Tvedt: X-RAY MICROANALYSIS OF BIOLOGICAL MATERIAL.
54. Tore C. Stiles: COGNITIVE VULNERABILITY FACTORS IN THE DEVELOPMENT AND MAINTENANCE OF DEPRESSION.
55. Eva Hofsli: TUMOR NECROSIS FACTOR AND MULTIDRUG RESISTANCE.
56. Helge S. Haarstad: TROPHIC EFFECTS OF CHOLECYSTOKININ AND SECRETIN ON THE RAT PANCREAS.
57. Lars Engebretsen: TREATMENT OF ACUTE ANTERIOR CRUCIATE LIGAMENT INJURIES.
58. Tarjei Rygnestad: DELIBERATE SELF-POISONING IN TRONDHEIM.
59. Arne Z. Henriksen: STUDIES ON CONSERVED ANTIGENIC DOMAINS ON MAJOR OUTER MEMBRANE PROTEINS FROM ENTEROBACTERIA.
60. Steinar Westin: UNEMPLOYMENT AND HEALTH: Medical and social consequences of a factory closure in a ten-year controlled follow-up study.
61. Ylva Sahlin: INJURY REGISTRATION, a tool for accident preventive work.
62. Helge Bjørnstad Pettersen: BIOSYNTHESIS OF COMPLEMENT BY HUMAN ALVEOLAR MACROPHAGES WITH SPECIAL REFERENCE TO SARCOIDOSIS.
63. Berit Schei: TRAPPED IN PAINFUL LOVE.
64. Lars J. Vatten: PROSPECTIVE STUDIES OF THE RISK OF BREAST CANCER IN A COHORT OF NORWEGIAN WOMAN.

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65. Kåre Bergh: APPLICATIONS OF ANTI-C5a SPECIFIC MONOCLONAL ANTIBODIES FOR THE ASSESSMENT OF COMPLEMENT ACTIVATION.
66. Svein Svenningsen: THE CLINICAL SIGNIFICANCE OF INCREASED FEMORAL ANTEVERSION.
67. Olbjørn Klepp: NONSEMINOMATOUS GERM CELL TESTIS CANCER: THERAPEUTIC OUTCOME AND PROGNOSTIC FACTORS.
68. Trond Sand: THE EFFECTS OF CLICK POLARITY ON BRAINSTEM AUDITORY EVOKED POTENTIALS AMPLITUDE, DISPERSION, AND LATENCY VARIABLES.

69. Kjetil B. Åsbakk: STUDIES OF A PROTEIN FROM PSORIATIC SCALE, PSO P27, WITH RESPECT TO ITS POTENTIAL ROLE IN IMMUNE REACTIONS IN PSORIASIS.
70. Arnulf Hestnes: STUDIES ON DOWN´S SYNDROME.
71. Randi Nygaard: LONG-TERM SURVIVAL IN CHILDHOOD LEUKEMIA.
72. Bjørn Hagen: THIO-TEPA.
73. Svein Anda: EVALUATION OF THE HIP JOINT BY COMPUTED TOMOGRAMPHY AND ULTRASONOGRAPHY.

1992

74. Martin Svartberg: AN INVESTIGATION OF PROCESS AND OUTCOME OF SHORT-TERM PSYCHODYNAMIC PSYCHOTHERAPY.
75. Stig Arild Slørdahl: AORTIC REGURGITATION.
76. Harold C Sexton: STUDIES RELATING TO THE TREATMENT OF SYMPTOMATIC NON-PSYCHOTIC PATIENTS.
77. Maurice B. Vincent: VASOACTIVE PEPTIDES IN THE OCULAR/FOREHEAD AREA.
78. Terje Johannessen: CONTROLLED TRIALS IN SINGLE SUBJECTS.
79. Turid Nilsen: PYROPHOSPHATE IN HEPATOCYTE IRON METABOLISM.
80. Olav Haraldseth: NMR SPECTROSCOPY OF CEREBRAL ISCHEMIA AND REPERFUSION IN RAT.
81. Eiliv Brenna: REGULATION OF FUNCTION AND GROWTH OF THE OXYNTIC MUCOSA.

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82. Gunnar Bovim: CERVICOGENIC HEADACHE.
83. Jarl Arne Kahn: ASSISTED PROCREATION.
84. Bjørn Naume: IMMUNOREGULATORY EFFECTS OF CYTOKINES ON NK CELLS.
85. Rune Wiseth: AORTIC VALVE REPLACEMENT.
86. Jie Ming Shen: BLOOD FLOW VELOCITY AND RESPIRATORY STUDIES.
87. Piotr Kruszewski: SUNCT SYNDROME WITH SPECIAL REFERENCE TO THE AUTONOMIC NERVOUS SYSTEM.
88. Mette Haase Moen: ENDOMETRIOSIS.
89. Anne Vik: VASCULAR GAS EMBOLISM DURING AIR INFUSION AND AFTER DECOMPRESSION IN PIGS.
90. Lars Jacob Stovner: THE CHIARI TYPE I MALFORMATION.
91. Kjell Å. Salvesen: ROUTINE ULTRASONOGRAPHY IN UTERO AND DEVELOPMENT IN CHILDHOOD.

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92. Nina-Beate Liabakk: DEVELOPMENT OF IMMUNOASSAYS FOR TNF AND ITS SOLUBLE RECEPTORS.
93. Sverre Helge Torp: *erb*B ONCOGENES IN HUMAN GLIOMAS AND MENINGIOMAS.
94. Olav M. Linaker: MENTAL RETARDATION AND PSYCHIATRY. Past and present.
95. Per Oscar Feet: INCREASED ANTIDEPRESSANT AND ANTIPANIC EFFECT IN COMBINED TREATMENT WITH DIXYRAZINE AND TRICYCLIC ANTIDEPRESSANTS.
96. Stein Olav Samstad: CROSS SECTIONAL FLOW VELOCITY PROFILES FROM TWO-DIMENSIONAL DOPPLER ULTRASOUND: Studies on early mitral blood flow.
97. Bjørn Backe: STUDIES IN ANTENATAL CARE.
98. Gerd Inger Ringdal: QUALITY OF LIFE IN CANCER PATIENTS.
99. Torvid Kiserud: THE DUCTUS VENOSUS IN THE HUMAN FETUS.
100. Hans E. Fjøsne: HORMONAL REGULATION OF PROSTATIC METABOLISM.
101. Eylert Brodtkorb: CLINICAL ASPECTS OF EPILEPSY IN THE MENTALLY RETARDED.
102. Roar Juul: PEPTIDERGIC MECHANISMS IN HUMAN SUBARACHNOID HEMORRHAGE.
103. Unni Syversen: CHROMOGRANIN A. Phsysiological and Clinical Role.

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104. Odd Gunnar Brakstad: THERMOSTABLE NUCLEASE AND THE *nuc* GENE IN THE DIAGNOSIS OF *Staphylococcus aureus* INFECTIONS.
105. Terje Engan: NUCLEAR MAGNETIC RESONANCE (NMR) SPECTROSCOPY OF PLASMA IN MALIGNANT DISEASE.
106. Kirsten Rasmussen: VIOLENCE IN THE MENTALLY DISORDERED.
107. Finn Egil Skjeldestad: INDUCED ABORTION: Timetrends and Determinants.
108. Roar Stenseth: THORACIC EPIDURAL ANALGESIA IN AORTOCORONARY BYPASS SURGERY.
109. Arild Faxvaag: STUDIES OF IMMUNE CELL FUNCTION *in mice infected with* MURINE RETROVIRUS.

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110. Svend Aakhus: NONINVASIVE COMPUTERIZED ASSESSMENT OF LEFT VENTRICULAR FUNCTION AND SYSTEMIC ARTERIAL PROPERTIES. Methodology and some clinical applications.
111. Klaus-Dieter Bolz: INTRAVASCULAR ULTRASONOGRAPHY.
112. Petter Aadahl: CARDIOVASCULAR EFFECTS OF THORACIC AORTIC CROSS-CLAMPING.
113. Sigurd Steinshamn: CYTOKINE MEDIATORS DURING GRANULOCYTOPENIC INFECTIONS.
114. Hans Stifoss-Hanssen: SEEKING MEANING OR HAPPINESS?
115. Anne Kvikstad: LIFE CHANGE EVENTS AND MARITAL STATUS IN RELATION TO RISK AND PROGNOSIS OF CANSER.
116. Torbjørn Grøntvedt: TREATMENT OF ACUTE AND CHRONIC ANTERIOR CRUCIATE LIGAMENT INJURIES. A clinical and biomechanical study.
117. Sigrid Hørven Wigers: CLINICAL STUDIES OF FIBROMYALGIA WITH FOCUS ON ETIOLOGY, TREATMENT AND OUTCOME.
118. Jan Schjøtt: MYOCARDIAL PROTECTION: Functional and Metabolic Characteristics of Two Endogenous Protective Principles.
119. Marit Martinussen: STUDIES OF INTESTINAL BLOOD FLOW AND ITS RELATION TO TRANSITIONAL CIRCULATORY ADAPATION IN NEWBORN INFANTS.
120. Tomm B. Müller: MAGNETIC RESONANCE IMAGING IN FOCAL CEREBRAL ISCHEMIA.
121. Rune Haaverstad: OEDEMA FORMATION OF THE LOWER EXTREMITIES.
122. Magne Børset: THE ROLE OF CYTOKINES IN MULTIPLE MYELOMA, WITH SPECIAL REFERENCE TO HEPATOCYTE GROWTH FACTOR.
123. Geir Smedslund: A THEORETICAL AND EMPIRICAL INVESTIGATION OF SMOKING, STRESS AND DISEASE: RESULTS FROM A POPULATION SURVEY.

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124. Torstein Vik: GROWTH, MORBIDITY, AND PSYCHOMOTOR DEVELOPMENT IN INFANTS WHO WERE GROWTH RETARDED *IN UTERO*.
125. Siri Forsmo: ASPECTS AND CONSEQUENCES OF OPPORTUNISTIC SCREENING FOR CERVICAL CANCER. Results based on data from three Norwegian counties.
126. Jon S. Skranes: CEREBRAL MRI AND NEURODEVELOPMENTAL OUTCOME IN VERY LOW BIRTH WEIGHT (VLBW) CHILDREN. A follow-up study of a geographically based year cohort of VLBW children at ages one and six years.
127. Knut Bjørnstad: COMPUTERIZED ECHOCARDIOGRAPHY FOR EVALUTION OF CORONARY ARTERY DISEASE.
128. Grethe Elisabeth Borchgrevink: DIAGNOSIS AND TREATMENT OF WHIPLASH/NECK SPRAIN INJURIES CAUSED BY CAR ACCIDENTS.
129. Tor Elsås: NEUROPEPTIDES AND NITRIC OXIDE SYNTHASE IN OCULAR AUTONOMIC AND SENSORY NERVES.
130. Rolf W. Gråwe: EPIDEMIOLOGICAL AND NEUROPSYCHOLOGICAL PERSPECTIVES ON SCHIZOPHRENIA.
131. Tonje Strømholm: CEREBRAL HAEMODYNAMICS DURING THORACIC AORTIC CROSSCLAMPING. An experimental study in pigs.

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132. Martinus Bråten: STUDIES ON SOME PROBLEMS REALTED TO INTRAMEDULLARY NAILING OF FEMORAL FRACTURES.
133. Ståle Nordgård: PROLIFERATIVE ACTIVITY AND DNA CONTENT AS PROGNOSTIC INDICATORS IN ADENOID CYSTIC CARCINOMA OF THE HEAD AND NECK.
134. Egil Lien: SOLUBLE RECEPTORS FOR **TNF** AND **LPS**: RELEASE PATTERN AND POSSIBLE SIGNIFICANCE IN DISEASE.
135. Marit Bjørgaas: HYPOGLYCAEMIA IN CHILDREN WITH DIABETES MELLITUS
136. Frank Skorpen: GENETIC AND FUNCTIONAL ANALYSES OF DNA REPAIR IN HUMAN CELLS.
137. Juan A. Pareja: SUNCT SYNDROME. ON THE CLINICAL PICTURE. ITS DISTINCTION FROM OTHER, SIMILAR HEADACHES.
138. Anders Angelsen: NEUROENDOCRINE CELLS IN HUMAN PROSTATIC CARCINOMAS AND THE PROSTATIC COMPLEX OF RAT, GUINEA PIG, CAT AND DOG.
139. Fabio Antonaci: CHRONIC PAROXYSMAL HEMICRANIA AND HEMICRANIA CONTINUA: TWO DIFFERENT ENTITIES?
140. Sven M. Carlsen: ENDOCRINE AND METABOLIC EFFECTS OF METFORMIN WITH SPECIAL EMPHASIS ON CARDIOVASCULAR RISK FACTORES.

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141. Terje A. Murberg: DEPRESSIVE SYMPTOMS AND COPING AMONG PATIENTS WITH CONGESTIVE HEART FAILURE.
142. Harm-Gerd Karl Blaas: THE EMBRYONIC EXAMINATION. Ultrasound studies on the development of the human embryo.
143. Noèmi Becser Andersen:THE CEPHALIC SENSORY NERVES IN UNILATERAL HEADACHES. Anatomical background and neurophysiological evaluation.
144. Eli-Janne Fiskerstrand: LASER TREATMENT OF PORT WINE STAINS. A study of the efficacy and limitations of the pulsed dye laser. Clinical and morfological analyses aimed at improving the therapeutic outcome.
145. Bård Kulseng: A STUDY OF ALGINATE CAPSULE PROPERTIES AND CYTOKINES IN RELATION TO INSULIN DEPENDENT DIABETES MELLITUS.
146. Terje Haug: STRUCTURE AND REGULATION OF THE HUMAN UNG GENE ENCODING URACIL-DNA GLYCOSYLASE.
147. Heidi Brurok: MANGANESE AND THE HEART. A Magic Metal with Diagnostic and Therapeutic Possibilites.
148. Agnes Kathrine Lie: DIAGNOSIS AND PREVALENCE OF HUMAN PAPILLOMAVIRUS INFECTION IN CERVICAL INTRAEPITELIAL NEOPLASIA. Relationship to Cell Cycle Regulatory Proteins and HLA DQBI Genes.
149. Ronald Mårvik: PHARMACOLOGICAL, PHYSIOLOGICAL AND PATHOPHYSIOLOGICAL STUDIES ON ISOLATED STOMACS.
150. Ketil Jarl Holen: THE ROLE OF ULTRASONOGRAPHY IN THE DIAGNOSIS AND TREATMENT OF HIP DYSPLASIA IN NEWBORNS.
151. Irene Hetlevik: THE ROLE OF CLINICAL GUIDELINES IN CARDIOVASCULAR RISK INTERVENTION IN GENERAL PRACTICE.
152. Katarina Tunòn: ULTRASOUND AND PREDICTION OF GESTATIONAL AGE.
153. Johannes Soma: INTERACTION BETWEEN THE LEFT VENTRICLE AND THE SYSTEMIC ARTERIES.
154. Arild Aamodt: DEVELOPMENT AND PRE-CLINICAL EVALUATION OF A CUSTOM-MADE FEMORAL STEM.
155. Agnar Tegnander: DIAGNOSIS AND FOLLOW-UP OF CHILDREN WITH SUSPECTED OR KNOWN HIP DYSPLASIA.
156. Bent Indredavik: STROKE UNIT TREATMENT: SHORT AND LONG-TERM EFFECTS
157. Jolanta Vanagaite Vingen: PHOTOPHOBIA AND PHONOPHOBIA IN PRIMARY HEADACHES

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158. Ola Dalsegg Sæther: PATHOPHYSIOLOGY DURING PROXIMAL AORTIC CROSS-CLAMPING CLINICAL AND EXPERIMENTAL STUDIES
159. xxxxxxxxx (blind number)
160. Christina Vogt Isaksen: PRENATAL ULTRASOUND AND POSTMORTEM FINDINGS – A TEN YEAR CORRELATIVE STUDY OF FETUSES AND INFANTS WITH DEVELOPMENTAL ANOMALIES.
161. Holger Seidel: HIGH-DOSE METHOTREXATE THERAPY IN CHILDREN WITH ACUTE LYMPHOCYTIC LEUKEMIA: DOSE, CONCENTRATION, AND EFFECT CONSIDERATIONS.
162. Stein Hallan: IMPLEMENTATION OF MODERN MEDICAL DECISION ANALYSIS INTO CLINICAL DIAGNOSIS AND TREATMENT.
163. Malcolm Sue-Chu: INVASIVE AND NON-INVASIVE STUDIES IN CROSS-COUNTRY SKIERS WITH ASTHMA-LIKE SYMPTOMS.
164. Ole-Lars Brekke: EFFECTS OF ANTIOXIDANTS AND FATTY ACIDS ON TUMOR NECROSIS FACTOR-INDUCED CYTOTOXICITY.
165. Jan Lundbom: AORTOCORONARY BYPASS SURGERY: CLINICAL ASPECTS, COST CONSIDERATIONS AND WORKING ABILITY.
166. John-Anker Zwart: LUMBAR NERVE ROOT COMPRESSION, BIOCHEMICAL AND NEUROPHYSIOLOGICAL ASPECTS.
167. Geir Falck: HYPEROSMOLALITY AND THE HEART.
168. Eirik Skogvoll: CARDIAC ARREST Incidence, Intervention and Outcome.
169. Dalius Bansevicius: SHOULDER-NECK REGION IN CERTAIN HEADACHES AND CHRONIC PAIN SYNDROMES.
170. Bettina Kinge: REFRACTIVE ERRORS AND BIOMETRIC CHANGES AMONG UNIVERSITY STUDENTS IN NORWAY.
171. Gunnar Qvigstad: CONSEQUENCES OF HYPERGASTRINEMIA IN MAN

172. Hanne Ellekjær: EPIDEMIOLOGICAL STUDIES OF STROKE IN A NORWEGIAN POPULATION. INCIDENCE, RISK FACTORS AND PROGNOSIS
173. Hilde Grimstad: VIOLENCE AGAINST WOMEN AND PREGNANCY OUTCOME.
174. Astrid Hjelde: SURFACE TENSION AND COMPLEMENT ACTIVATION: Factors influencing bubble formation and bubble effects after decompression.
175. Kjell A. Kvistad: MR IN BREAST CANCER – A CLINICAL STUDY.
176. Ivar Rossvoll: ELECTIVE ORTHOPAEDIC SURGERY IN A DEFINED POPULATION. Studies on demand, waiting time for treatment and incapacity for work.
177. Carina Seidel: PROGNOSTIC VALUE AND BIOLOGICAL EFFECTS OF HEPATOCYTE GROWTH FACTOR AND SYNDECAN-1 IN MULTIPLE MYELOMA.

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178. Alexander Wahba: THE INFLUENCE OF CARDIOPULMONARY BYPASS ON PLATELET FUNCTION AND BLOOD COAGULATION – DETERMINANTS AND CLINICAL CONSEQUENSES
179. Marcus Schmitt-Egenolf: THE RELEVANCE OF THE MAJOR hISTOCOMPATIBILITY COMPLEX FOR THE GENETICS OF PSORIASIS
180. Odrun Arna Gederaas: BIOLOGICAL MECHANISMS INVOLVED IN 5-AMINOLEVULINIC ACID BASED PHOTODYNAMIC THERAPY
181. Pål Richard Romundstad: CANCER INCIDENCE AMONG NORWEGIAN ALUMINIUM WORKERS
182. Henrik Hjorth-Hansen: NOVEL CYTOKINES IN GROWTH CONTROL AND BONE DISEASE OF MULTIPLE MYELOMA
183. Gunnar Morken: SEASONAL VARIATION OF HUMAN MOOD AND BEHAVIOUR
184. Bjørn Olav Haugen: MEASUREMENT OF CARDIAC OUTPUT AND STUDIES OF VELOCITY PROFILES IN AORTIC AND MITRAL FLOW USING TWO- AND THREE-DIMENSIONAL COLOUR FLOW IMAGING
185. Geir Bråthen: THE CLASSIFICATION AND CLINICAL DIAGNOSIS OF ALCOHOL-RELATED SEIZURES
186. Knut Ivar Aasarød: RENAL INVOLVEMENT IN INFLAMMATORY RHEUMATIC DISEASE. A Study of Renal Disease in Wegener's Granulomatosis and in Primary Sjögren's Syndrome
187. Trude Helen Flo: RESEPTORS INVOLVED IN CELL ACTIVATION BY DEFINED URONIC ACID POLYMERS AND BACTERIAL COMPONENTS
188. Bodil Kavli: HUMAN URACIL-DNA GLYCOSYLASES FROM THE UNG GENE: STRUCTRUAL BASIS FOR SUBSTRATE SPECIFICITY AND REPAIR
189. Liv Thommesen: MOLECULAR MECHANISMS INVOLVED IN TNF- AND GASTRIN-MEDIATED GENE REGULATION
190. Turid Lingaas Holmen: SMOKING AND HEALTH IN ADOLESCENCE; THE NORD-TRØNDELAG HEALTH STUDY, 1995-97
191. Øyvind Hjertner: MULTIPLE MYELOMA: INTERACTIONS BETWEEN MALIGNANT PLASMA CELLS AND THE BONE MICROENVIRONMENT
192. Asbjørn Støylen: STRAIN RATE IMAGING OF THE LEFT VENTRICLE BY ULTRASOUND. FEASIBILITY, CLINICAL VALIDATION AND PHYSIOLOGICAL ASPECTS
193. Kristian Midthjell: DIABETES IN ADULTS IN NORD-TRØNDELAG. PUBLIC HEALTH ASPECTS OF DIABETES MELLITUS IN A LARGE, NON-SELECTED NORWEGIAN POPULATION.
194. Guanglin Cui: FUNCTIONAL ASPECTS OF THE ECL CELL IN RODENTS
195. Ulrik Wisløff: CARDIAC EFFECTS OF AEROBIC ENDURANCE TRAINING: HYPERTROPHY, CONTRACTILITY AND CALCUIM HANDLING IN NORMAL AND FAILING HEART
196. Øyvind Halaas: MECHANISMS OF IMMUNOMODULATION AND CELL-MEDIATED CYTOTOXICITY INDUCED BY BACTERIAL PRODUCTS
197. Tore Amundsen: PERFUSION MR IMAGING IN THE DIAGNOSIS OF PULMONARY EMBOLISM
198. Nanna Kurtze: THE SIGNIFICANCE OF ANXIETY AND DEPRESSION IN FATIQUE AND PATTERNS OF PAIN AMONG INDIVIDUALS DIAGNOSED WITH FIBROMYALGIA: RELATIONS WITH QUALITY OF LIFE, FUNCTIONAL DISABILITY, LIFESTYLE, EMPLOYMENT STATUS, CO-MORBIDITY AND GENDER
199. Tom Ivar Lund Nilsen: PROSPECTIVE STUDIES OF CANCER RISK IN NORD-TRØNDELAG: THE HUNT STUDY. Associations with anthropometric, socioeconomic, and lifestyle risk factors
200. Asta Kristine Håberg: A NEW APPROACH TO THE STUDY OF MIDDLE CEREBRAL ARTERY OCCLUSION IN THE RAT USING MAGNETIC RESONANCE TECHNIQUES

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201. Knut Jørgen Arntzen: PREGNANCY AND CYTOKINES
202. Henrik Døllner: INFLAMMATORY MEDIATORS IN PERINATAL INFECTIONS
203. Asta Bye: LOW FAT, LOW LACTOSE DIET USED AS PROPHYLACTIC TREATMENT OF ACUTE INTESTINAL REACTIONS DURING PELVIC RADIOTHERAPY. A PROSPECTIVE RANDOMISED STUDY.
204. Sylvester Moyo: STUDIES ON STREPTOCOCCUS AGALACTIAE (GROUP B STREPTOCOCCUS) SURFACE-ANCHORED MARKERS WITH EMPHASIS ON STRAINS AND HUMAN SERA FROM ZIMBABWE.
205. Knut Hagen: HEAD-HUNT: THE EPIDEMIOLOGY OF HEADACHE IN NORD-TRØNDELAG
206. Li Lixin: ON THE REGULATION AND ROLE OF UNCOUPLING PROTEIN-2 IN INSULIN PRODUCING ß-CELLS
207. Anne Hildur Henriksen: SYMPTOMS OF ALLERGY AND ASTHMA VERSUS MARKERS OF LOWER AIRWAY INFLAMMATION AMONG ADOLESCENTS
208. Egil Andreas Fors: NON-MALIGNANT PAIN IN RELATION TO PSYCHOLOGICAL AND ENVIRONTENTAL FACTORS. EXPERIENTAL AND CLINICAL STUDES OF PAIN WITH FOCUS ON FIBROMYALGIA
209. Pål Klepstad: MORPHINE FOR CANCER PAIN
210. Ingunn Bakke: MECHANISMS AND CONSEQUENCES OF PEROXISOME PROLIFERATOR-INDUCED HYPERFUNCTION OF THE RAT GASTRIN PRODUCING CELL
211. Ingrid Susann Gribbestad: MAGNETIC RESONANCE IMAGING AND SPECTROSCOPY OF BREAST CANCER
212. Rønnaug Astri Ødegård: PREECLAMPSIA – MATERNAL RISK FACTORS AND FETAL GROWTH
213. Johan Haux: STUDIES ON CYTOTOXICITY INDUCED BY HUMAN NATURAL KILLER CELLS AND DIGITOXIN
214. Turid Suzanne Berg-Nielsen: PARENTING PRACTICES AND MENTALLY DISORDERED ADOLESCENTS
215. Astrid Rydning: BLOOD FLOW AS A PROTECTIVE FACTOR FOR THE STOMACH MUCOSA. AN EXPERIMENTAL STUDY ON THE ROLE OF MAST CELLS AND SENSORY AFFERENT NEURONS

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216. Jan Pål Loennechen: HEART FAILURE AFTER MYOCARDIAL INFARCTION. Regional Differences, Myocyte Function, Gene Expression, and Response to Cariporide, Losartan, and Exercise Training.
217. Elisabeth Qvigstad: EFFECTS OF FATTY ACIDS AND OVER-STIMULATION ON INSULIN SECRETION IN MAN
218. Arne Åsberg: EPIDEMIOLOGICAL STUDIES IN HEREDITARY HEMOCHROMATOSIS: PREVALENCE, MORBIDITY AND BENEFIT OF SCREENING.
219. Johan Fredrik Skomsvoll: REPRODUCTIVE OUTCOME IN WOMEN WITH RHEUMATIC DISEASE. A population registry based study of the effects of inflammatory rheumatic disease and connective tissue disease on reproductive outcome in Norwegian women in 1967-1995.
220. Siv Mørkved: URINARY INCONTINENCE DURING PREGNANCY AND AFTER DELIVERY: EFFECT OF PELVIC FLOOR MUSCLE TRAINING IN PREVENTION AND TREATMENT
221. Marit S. Jordhøy: THE IMPACT OF COMPREHENSIVE PALLIATIVE CARE
222. Tom Christian Martinsen: HYPERGASTRINEMIA AND HYPOACIDITY IN RODENTS – CAUSES AND CONSEQUENCES
223. Solveig Tingulstad: CENTRALIZATION OF PRIMARY SURGERY FOR OVARAIN CANCER. FEASIBILITY AND IMPACT ON SURVIVAL
224. Haytham Eloqayli: METABOLIC CHANGES IN THE BRAIN CAUSED BY EPILEPTIC SEIZURES
225. Torunn Bruland: STUDIES OF EARLY RETROVIRUS-HOST INTERACTIONS – VIRAL DETERMINANTS FOR PATHOGENESIS AND THE INFLUENCE OF SEX ON THE SUSCEPTIBILITY TO FRIEND MURINE LEUKAEMIA VIRUS INFECTION
226. Torstein Hole: DOPPLER ECHOCARDIOGRAPHIC EVALUATION OF LEFT VENTRICULAR FUNCTION IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION
227. Vibeke Nossum: THE EFFECT OF VASCULAR BUBBLES ON ENDOTHELIAL FUNCTION
228. Sigurd Fasting: ROUTINE BASED RECORDING OF ADVERSE EVENTS DURING ANAESTHESIA – APPLICATION IN QUALITY IMPROVEMENT AND SAFETY
229. Solfrid Romundstad: EPIDEMIOLOGICAL STUDIES OF MICROALBUMINURIA. THE NORD-TRØNDELAG HEALTH STUDY 1995-97 (HUNT 2)

230. Geir Torheim: PROCESSING OF DYNAMIC DATA SETS IN MAGNETIC RESONANCE IMAGING
231. Catrine Ahlén: SKIN INFECTIONS IN OCCUPATIONAL SATURATION DIVERS IN THE NORTH SEA AND THE IMPACT OF THE ENVIRONMENT
232. Arnulf Langhammer: RESPIRATORY SYMPTOMS, LUNG FUNCTION AND BONE MINERAL DENSITY IN A COMPREHENSIVE POPULATION SURVEY. THE NORD-TRØNDELAG HEALTH STUDY 1995-97. THE BRONCHIAL OBSTRUCTION IN NORD-TRØNDELAG STUDY
233. Einar Kjelsås: EATING DISORDERS AND PHYSICAL ACTIVITY IN NON-CLINICAL SAMPLES
234. Arne Wibe: RECTAL CANCER TREATMENT IN NORWAY – STANDARDISATION OF SURGERY AND QUALITY ASSURANCE

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235. Eivind Witsø: BONE GRAFT AS AN ANTIBIOTIC CARRIER
236. Anne Mari Sund: DEVELOPMENT OF DEPRESSIVE SYMPTOMS IN EARLY ADOLESCENCE
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