Øivind Rognmo

# High-intensity aerobic exercise and cardiovascular health

Thesis for the degree of Doctor Philosophiae

Trondheim, December 2008

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

NTNU
Norwegian University of
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ISBN 978-82-471-1359-2 (printed ver.)
ISBN 978-82-471-1360-8 (electronic ver.)
ISSN 1503-8181

Doctoral theses at NTNU, 2008:325

Printed by NTNU-trykk

# Aerob høyintensitetstrening og kardiovaskulær helse

Regelmessig fysisk aktivitet bedrer den fysiske formen, og er dokumentert å være en viktig bidragsyter med tanke på å redusere forekomsten av sykdom og dødelighet. Det maksimale oksygenopptaket, som er det beste målet på arbeidskapasitet, er vist å være en svært sterk indikator på dødelighet både hos friske og hos pasienter med hjerte-karsykdom. Regelmessig utholdenhetstrening for å øke maksimalt oksygenopptak er derfor anbefalt for bedret helse og økt livslengde. Selv om dette er etablert kunnskap, vet man lite om hvilken intensitet kondisjonstreningen bør gjennomføres med for å oppnå best mulig helsegevinst.

Hensikten med denne doktorgradsavhandlingen var derfor å kartlegge hvilken intensitet i kondisjonstreningen som gir best effekt med tanke på å øke det maksimale oksygenopptaket blant pasienter med koronarsykdom. Vi ønsket også å studere hvorvidt intensiteten er viktig for å bedre fysisk form og redusere risikofaktorer for hjerte-karsykdom hos pasienter med metabolsk syndrom, som har en sterk opphopning av disse risikofaktorene. Derfor sammenliknet vi aerob intervalltrening med høy intensitet (80-90 % av maksimalt oksygenopptak) med kontinuerlig kondisjonstrening med moderat intensitet (50-60 % av maksimalt oksygenopptak) der total treningsmengde var lik. Videre ønsket vi å undersøke hvordan blodårenes funksjon og elastisitet ble påvirket av ulik type trening, både blant unge trente og utrente, og blant pasienter med metabolsk syndrom.

Resultatene viste at trening med høy intensitet ga bedre effekter enn moderat intensitet for å bedre aerob kapasitet og redusere kjente risikofaktorer forbundet med hjerte-karsykdom, inkludert blodårefunksjonen. Avhandlingen kan derfor bidra med ny innsikt med tanke på bruk av aerob intervalltrening for mer effektivt å bedre kondisjonen og dermed helsen, både blant hjertesyke og hos individer med forhøyet risiko for fremtidig hjerte-karsykdom.

**Øivind Rognmo**

Institutt for Sirkulasjon og Bildediagnostikk, Det Medisinske Fakultet, NTNU
Veiledere: Professor Stig A. Slørdahl og Professor Jan Helgerud (biveileder)
Finansieringskilde: NTNU og St.Olavs Hospital - Universitetssykehuset i Trondheim

*Ovennevnte avhandling er funnet verdig til å forsvares offentlig*
*for graden doctor philosophiae*
*Disputas finner sted i Auditoriet, Medisinsk Teknisk Forskningssenter, NTNU*
*Mandag 15. desember 2008 kl.1315*

## CONTENTS

## ACKNOWLEDGEMENTS

The present dr. philos. project was carried out during the years 2002-2004 at the Department of Circulation and Medical Imaging, Faculty of Medicine, Norwegian University of Science and Technology (NTNU). The financial support was granted by St. Olavs Hospital, Trondheim, Norway, and from NTNU, and is gratefully acknowledged.

I would like to express my gratitude to my supervisor, Professor Stig A. Slørdahl, who believed in me for this project. I am thankful for your guidance and for that you allowed me to resume my position to complete my thesis after four years break to function as technical chief of the Norwegian Alpine Men's Ski Team.

I would also thank my co-supervisor Professor Jan Helgerud and Professor Jan Hoff for all advices and for introducing me to the field of science and sports medicine. A special gratitude goes to Jan Hoff who has really contributed to forming my paths, being a catalyst to both my science- and my coaching career.

Professor Ulrik Wisløff deserves a huge recognition for his contribution in my projects and for his great expertise as an advisor, motivator and comrade.

I have had a lot of good colleagues through the years and I have really appreciated to work and discuss with Brage H. Amundsen, Morten A. Høydal, Ole J. Kemi, Eva Veslemøy Tyldum, Aud Hiller, Ragna Elise Støre Govatsmark and Trine Moholdt. A special salute goes to the office guys; Arnt Erik Tjønna, Tomas Stølen, Eivind Brønstad and Harald Edvard Mølmen Hansen.

Thank you Kari and Jan for being wonderful parents and giving me the best upbringing and advices. It was great growing up in Narvik together with Morten, my identical twin-brother who I feel very close to. I will also send a hug to his wife Ingvild and to my nieces Vilde and Martine. Thank you also Grandma Claudia and Turid.

Finally, I would thank my wife and greatest love Cathrine. Your love and support is inestimable to me.

Trondheim, August 2008

Øivind Rognmo

## PREFACE

The study presented in this thesis was carried out at the Department of Circulation and Medical Imaging, Faculty of Medicine, Norwegian University of Science and Technology, and at the Department of Cardiology, St. Olavs Hospital, Trondheim University Hospital. The included original papers listed below are referred to by their roman number throughout the thesis.

**Paper I**

High intensity aerobic interval exercise is superior to moderate intensity exercise for increasing aerobic capacity in patients with coronary artery disease. Ø Rognmo, EV Hetland, J Helgerud, J Hoff, SA Slørdahl. *European Journal of Cardiovascular Prevention and Rehabilitation.* 2004;11:216-222

**Paper II**

Endothelial function in highly endurance-trained and sedentary, healthy young women. IT Moe, H Hoven, EV Hetland, Ø Rognmo, SA Slørdahl. *Vascular Medicine.* 2005;10:97-102.

**Paper III**

Endothelial function in highly endurance-trained men: Effects of acute exercise.
Ø Rognmo, TH Bjørnstad, C Kahrs, AE Tjønna, A Bye, PM Haram, T Stølen, SA Slørdahl, U Wisløff. *Journal of Strength and Conditioning Research.* 2008;22:535-542.

**Paper IV**

Aerobic interval training vs. continuous moderate exercise as a treatment for the metabolic syndrome - “A Pilot Study”. AE Tjønna, SJ Lee, Ø Rognmo, T Stølen, A Bye, PM Haram, JP Loennechen, QY Al-Share, E Skogvoll, SA Slørdahl, OJ Kemi, SM Najjar, U Wisløff. *Circulation.* 2008;118:346-54.

## DEFINITIONS

**Physical activity:** Any bodily movement produced by skeletal muscles that result in energy expenditure beyond resting expenditure.

**Physical fitness:** Includes cardiorespiratory fitness, muscle strength, body composition, and flexibility, comprising a set of attributes that people have or achieve that relates to the ability to perform physical work.

**Cardiorespiratory endurance:** The ability to perform dynamic large-muscle, whole body exercise at moderate to high intensities over a longer period

**Exercise training:** A subset of physical activity that is planned, structured, repetitive, and purposeful in the sense that improvement or maintenance of physical fitness is the objective.

**Maximal oxygen uptake ($VO_{2max}$):** The highest rate at which oxygen can be taken up in the body during strenuous dynamically exercise with large muscle groups. It is considered the best measure of cardiorespiratory endurance since it sets the upper limit of aerobic capacity.

**Aerobic capacity:** Equivalent to $VO_{2max}$.

**Cardiovascular disease (CVD):** Diseases of the heart and the circulatory system.

**Coronary artery disease (CAD):** The accumulation of atheromatous plaques within the walls of the arteries that supply the myocardium.

**Metabolic syndrome:** The clustering of risk factors for cardiovascular disease. The most common combinations of risk factors found among patients with the syndrome are obesity, impaired glucose tolerance or insulin resistance, hypertension, dyslipidaemia and low HDL-cholesterol.

**Flow-mediated dilatation (FMD):** Reactive hyperaemia-induced increase in blood flow and shear stress that causes dilatation that can be quantified as an index of endothelial function.

## ABBREVIATIONS

| | |
|---|---|
| ATP | Adenosine triphosphate |
| $BH_4$ | Tetrahydrobiopterin |
| BMI | Body mass index |
| BSA | Body surface area |
| CABG | Coronary artery bypass graft surgery |
| CAD | Coronary artery disease |
| CaM | Calmodulin |
| cGMP | Cyclic guanosine monophosphate |
| CHD | Coronary heart disease |
| CI | Confidence interval |
| CVD | Cardiovascular disease |
| ECG | Electrocardiogram |
| EDHF | Endothelial derived hyperpolarising factor |
| eNOS | Endothelial nitric oxide synthase |
| EPC | Endothelial progenitor cell |
| FMD | Flow-mediated dilatation |
| GC | Guanylate cyclase |
| GTN | Glycerol trinitrate |
| $H^+$ | Hydrogen ion |
| HDL | High density lipoprotein |
| $HR_{max}$ | Maximal heart rate |
| LDL | Low density lipoprotein |
| L-NAME | L-nitroarginine methylester |
| L-NMMA | L-$N^G$-monomethyl arginine |
| NADPH | Nicotinamide adenine dinucleotide phosphate |
| NO | Nitric oxide |
| PCI | Percutaneous coronary intervention |
| RER | Respiratory exchange ratio |
| VEGF | Vascular endothelial growth factor |
| $VO_{2max}$ | Maximal oxygen uptake |
| WHO | World health organisation |

# INTRODUCTION

Diseases of the heart and the circulatory system (cardiovascular disease or CVD) are the leading cause of death in Europe with 4.3 million deaths per year (1). Despite a general declining trend in CVD mortality in Western, Northern and Southern European countries the last years, CVD still causes nearly half (48%) of all European deaths. Just under half of all deaths from CVD are from coronary artery disease (CAD) and nearly one third is from stroke (1). The CVD mortality rate in Norway has decreased the past decades with the percentage share of CVD mortality declining from 46% in 1991 to 35% in 2005 (2), probably due to improved medical and surgical treatment (3). Today we know that physical activity is an effective contributor for reducing both total and CVD mortality disease, and should therefore play a natural part of everyday life (4-6).

## Exercise and health

Regular physical activity involving large muscle groups produces cardiovascular adaptations that increase physical fitness. Higher levels of physical activity and fitness are known to reduce both all-cause mortality and CVD mortality (4-11). Physical exercise is thus strongly recommended in both primary and secondary prevention of CVD (12-16). In addition to reducing mortality, there is also evidence that increasing physical fitness will improve health (17) and reduce the risk of a number of chronic diseases such as CVD (18), type 2 diabetes (19), osteoporosis (20), obesity (21), depression (22) and cancer of the breast and colon (23).

## Cardiorespiratory endurance

Cardiorespiratory endurance is one of the fundamental components of physical fitness (24) and has been defined as the ability to dynamically perform large-muscle, whole body exercise at moderate to high intensities over a longer period (25). The three major factors limiting cardiorespiratory endurance are maximal oxygen uptake, lactate threshold and work economy (25,26). To increase endurance performance one have to increase at least one of these factors.

### Maximal oxygen uptake

The oxygen uptake is a measure of aerobic energy turnover in the body, and reflects the capacity to transport and utilise oxygen, i.e. the functional capacity of the lungs,

cardiovascular system and muscle mitochondria combined (27). Maximal oxygen uptake ($VO_{2max}$) is defined as the highest rate at which oxygen can be taken up in the body during severe exercise with large muscle groups (28). It is considered as the best measure of cardiorespiratory endurance since it sets the upper limit of aerobic capacity (29). $VO_{2max}$ is the product of oxygen delivery and arteriovenous oxygen difference. In both athletes and healthy individuals $VO_{2max}$ is limited by the ability of the cardiorespiratory system to supply the working muscles with oxygen (27-32). It is important to emphasise that each and every step in the oxygen supply pathway from the lungs to the mitochondria contributes to determine $VO_{2max}$ but that the major influence is set by cardiac output, or more precisely stroke volume since maximal heart rate is fixed (27,28). However, untrained individuals and patients may be limited by the metabolic demand of the muscle mitochondria and it is suggested that exercise training may induce a switch from demand to supply limitation of $VO_{2max}$ (33).

**Lactate threshold**

During exercise with continuously increasing power output, lactate production will reach a point where lactate release into the blood rises faster than the clearance mechanisms in muscle and other tissues can accommodate. This inflection point in blood lactate level is named the lactate threshold and determines the fraction of $VO_2$ that may be sustained for an extended period of time (34). The main factors responsible for lactate accumulation appear to be recruitment of fast-contracting muscle fibers, secretion of hormones that accelerate glycogenolysis and glycolysis, and a redistribution of blood flow from lactate-removing tissues to lactate-producing tissues (34).

**Work economy**

Work economy is defined as the oxygen uptake needed to work at a given intensity (25). Task specific endurance training will improve work economy (35). Interestingly, also maximal strength training has shown to improve work economy in endurance events, because an increase in maximal strength will lead to improved neuromuscular characteristics of the working muscles, which save oxygen during submaximal work (36-38).

### Aerobic exercise training responses

Aerobic exercise training improves cardiorespiratory endurance by inducing changes in both oxygen transport and utilisation. Maximal oxygen delivery increases after aerobic training due to an increase in stroke volume, myocardial contractility and blood volume (39-41). Also, the arteriovenous oxygen difference in the skeletal muscles improves due to increases in mitochondrial density, oxidative enzyme concentration, capillary density, myoglobin- and glycogen concentration (15,29,34,42).

## Health effects of improved aerobic capacity

### Cardiovascular disease

Aerobic exercise training has special significance for individuals with CVD because the exercise-induced changes promote lower myocardial oxygen demand at any given workload. These include reduced heart rate, lower systolic blood pressure, and decreased amount of circulating catecholamines (15). The benefits of these adjustments can be demonstrated by the greater amount of work that can be done before angina pectoris and/or ischemic ST depression occurs. Also, myocardial perfusion has been found to improve after aerobic exercise training among these patients (43,44). Individuals who participate in regular physical exercise possess a lower prevalence of cardiovascular risk factors such as hypertension (45), type 2 diabetes (19), obesity and hypercholesterolemia (46), and aerobic exercise is therefore considered an important adjuvant therapy in risk factor modification (16).

Peak aerobic exercise capacity is found to be a strong, independent predictor of both cardiac- and all-cause deaths among both healthy individuals and those with CVD (47-52). These findings indicate that increasing exercise capacity should make a difference not only in functional capacity but also in survival prognosis. In fact, in both healthy subjects and those with CVD, the peak exercise capacity is shown to be a stronger predictor of increased risk of death compared to the established risk factors hypertension, obesity, smoking and type 2 diabetes (48). An important aspect is that poor physical fitness is a modifiable risk factor, and improvements in aerobic capacity has shown to reduce the risk of death (53).

In addition to prospective epidemiological studies, several meta-analyses have concluded that cardiac rehabilitation involving exercise reduces mortality rates in CAD patients (9-11). In the most recent meta-analysis, 48 randomized controlled trials of exercise-based cardiac rehabilitation were included (54). The studies included 8940 men and women of all ages. Studies were considered eligible if they were randomised controlled trials with follow-up of six months or more, with supervised or unsupervised exercise training of at least six months duration. Patients were included if they had sustained a myocardial infarction, had undergone coronary artery bypass grafting or percutaneous coronary intervention (PCI), had angina pectoris, or had CAD identified by angiography. Cardiac rehabilitation was associated with 20% reduced all-cause mortality and a 26% reduction in cardiac mortality. There was no difference in mortality between exercise-only cardiac rehabilitation and comprehensive cardiac rehabilitation, or by exercise dose or duration of follow-up (54). Exercise is thus associated with 20-26% decreased risk of mortality, i.e. a magnitude similar to that associated with antihypertensive and lipid lowering interventions (55,56).

Although several studies have shown a significant inverse relationship between participation in rehabilitation programmes involving exercise and reduced progression of CVD (57-61), data establishing which exercise-intensity that yields maximal beneficial adaptations are scarce. For health promotions, patients with CVD are recommended to regularly exercise at intensities ranging from 40-85% of $VO_{2max}$ (12-15,62). The Norwegian Directorate of Health recommends all adults to perform a minimum of 30 minutes of physical activity every day, at moderate to high intensity (63). However, aerobic exercise training programmes are most often carried out at low- to moderate intensities (64). Both walking and vigorous exercise have been found equally effective in increasing aerobic capacity and reducing cardiovascular event risk (65,66). However, two large cohort studies found that higher intensity of physical activity was related to reduced cardiovascular risk, as reflected by an inverse association between exercise intensity and coronary heart disease incidence in men (67,68).

**Metabolic syndrome**

The clustering of several metabolic and cardiovascular disease risk factors has been termed the metabolic syndrome. It is a common metabolic disorder that results from the increasing prevalence of obesity (69,70). When grouped together the risk factors are associated with increased risk of cardiovascular disease (71). Interestingly, a study by Wisløff et al. (72) demonstrated that after 11 generations of breeding of rats selected on low and high intrinsic exercise capacity, rats with low aerobic capacity scored high on cardiovascular risk factors that constitute the metabolic syndrome, i.e. linking reduced fitness to cardiovascular and metabolic disease. Several definitions of the metabolic syndrome are in use, but the most common combinations of risk factors found among individuals with the syndrome are obesity, impaired glucose tolerance or insulin resistance, hypertension, dyslipidaemia and low HDL-cholesterol (73). In order to overcome the problems related to the definition of the metabolic syndrome, a WHO working group in 1998 suggested a working definition of the metabolic syndrome. The WHO criteria of the syndrome (74) are shown in table 1. Also, In 2006, a new world wide definition was created so that data from different countries more easily could be compared (75).

Table 1. WHO definition of the metabolic syndrome.

| |
|---|
| Glucose intolerance or diabetes and/or insulin resistance |
| + 2 of the following: |
| Obesity; BMI >30 kg/$m^2$ and or waist-to hip-ration >0.9 (♂) or >0.85 (♀) |
| Dyslipidaemia; triglycerides >1.7mmol/l and/or HDL cholesterol <0.9 (♂), <1.0 (♀) |
| Hypertension; Blood pressure >140/90 and/or medication |
| Microalbuminuria; albumin excretion >20µg/min |

Lakka et al. (76) reported that middle-aged Finnish men diagnosed with metabolic syndrome as defined by the WHO had 2.5 (CI: 1.3-4.8) times higher CVD mortality and 1.9 (CI: 1.2-2.9) times higher all-cause mortality over 11.6 years of follow-up than healthy men. The same conclusion was made by Katzmarkzyk et al. (77) who found that American men diagnosed with the metabolic syndrome were 1.3 (CI: 1.1-1.6) times more likely to die of any cause and 1.9 (CI: 1.4-2.6) times more likely to die of

CVD than healthy men after adjustment for age, year of examination, smoking status, alcohol consumption, and parental CVD. They also found that higher levels of cardiorespiratory fitness attenuated the mortality risk as there was a substantially lower risk in fit men than in unfit men (77). The finding of a dose-response relationship between fitness and mortality indicate that physical activity may be a valuable treatment of the metabolic syndrome. The positive influence of aerobic exercise on metabolic syndrome in humans was shown by Katzmarkzyk et al. (78) who exercised 105 patients for 20 weeks. After the aerobic exercise training period was finished, 30% of the participants were no longer classified as having the metabolic syndrome.

Also among children the prevalence of obesity is increasing rapidly (79). In a study including 82 overweight or obese children it was shown that the vascular dysfunction associated with obesity in children is partially reversible by 1 year of dietary modification (80). In a recent study by Tjønna et al. (81) it was found that three months of two weekly high-intensity aerobic exercise sessions reduced several known cardiovascular risk factors, like endothelial dysfunction, $VO_{2max}$, insulin, fasting glucose and fat mass more than that observed after a multi-treatment strategy in obese adolescents. In addition, 12 months follow-up confirmed that high-intensity aerobic exercise was superior of improving or stabilising these risk factors.

**Safety of exercise**

Even if regular physical activity reduces coronary heart disease (CHD) events, vigorous activity can also acutely and transiently increase the risk of sudden cardiac death and acute myocardial infarction in susceptible persons (82-84). The risk of myocardial infarction during or soon after exertion is greater in persons who do not regularly participate in physical activity (83-85) and it is thus of great importance to get this sedentary group more active. The 2007 Scientific Statement from the American Heart Association on exercise and acute cardiovascular events (86) estimates one cardiac arrest per 116 906 patient-hours, one myocardial infarction per 219 970 patient-hours, one fatality per 752 365 patient-hours, and one major complication per 81 670 patient-hours of exercise in CHD-patients. Hauer et al. (87) demonstrated that adherence to prescribed target heart rate up to 95% of maximum (90% $VO_{2max}$) reached during symptom-limited exercise testing is associated with

very few ischemic episodes even during high-intensity exercise training in stable CAD-patients. However, exercise testing should be performed at the discretion of a physician before vigorous exercise in patients with known cardiovascular problems (18), and more studies are needed for safety evaluation of high-intensity exercise.

## Endothelial function

The vascular endothelium is the single layer of cells that form the inner lining of the cardiovascular system. It forms the biologic interface between circulating blood and the various organs of the body. Together with neural control, the endothelium is the major regulator of the vascular homeostasis by synthesising and releasing a number of biologically active factors involved in regulation of vascular tone and exerts anticoagulant, antiplatelet and fibrinolytic properties. The endothelial maintenance of vascular tone is accomplished by numerous vasodilators (e.g. nitric oxide (NO), endothelium-derived hyperpolarizing factor (EDHF), prostacyclin and bradykinin) and vasoconstrictors (e.g. endothelin-1 and angiotensin II) (88).

NO is probably the most important endothelial-derived relaxing factor. It is synthesised from the amino acid L-arginine to NO and L-citrulline by the enzyme endothelial nitric oxide synthase (eNOS) which is located in caveolae in cell membranes (88,89) (Figure 1). NO exerts its relaxing effects on vascular smooth muscle cells following stimulation by either shear stress or endothelial agonists such as bradykinin or acetylcholine by activating guanylate cyclase which increase production of cyclic guanosine monophosphate (cGMP) and decrease intracellular calcium (90). In addition to relaxing smooth muscle, NO counteracts events or actions that promote atherosclerosis, such as vasoconstriction, platelet aggregation, smooth muscle cell proliferation and migration, leukocyte adhesion, and oxidative stress (91). Another important endothelial-derived relaxing factor is prostacyclin, which acts synergistically with NO to inhibit platelet aggregation and contributes to exercise-induced hyperaemia (92,93). It seems that prostacyclin is a particularly important regulator of metabolic vasodilatation in patients with atherosclerosis, i.e. when NO production is reduced (94,95). EDHF is also known to be released by endothelial cells in response to shear stress but little is known about its physiological significance in humans (96).

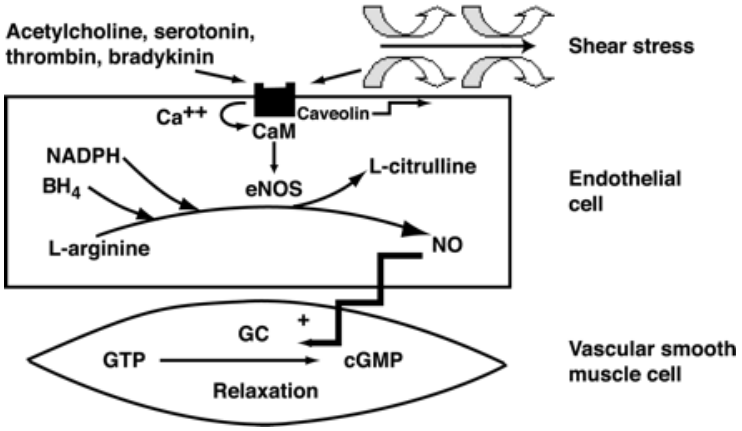


**Figure 1.** Production of NO by endothelial cells. NO is produced by the action of eNOS on L-arginine. This reaction requires a number of cofactors, including tetrahydrobiopterin ($BH_4$) and nicotinamide adenine dinucleotide phosphate (NADPH). Increased intercellular $Ca^{2+}$ in response to vasodilator agonists or shear stress displaces the inhibitor caveolin from calmodulin (CaM), activating eNOS. NO diffuses to vascular smooth muscle and causes relaxation by activating guanylate cyclase (GC), thereby increasing intracellular cyclic guanosine monophosphate (cGMP). Reprinted from Davignon and Ganz. *Circulation* 2004;109(23 Suppl 1):III27-32.

Endothelin-1, the most prominent vasoconstrictor secreted by the endothelium has been linked to the etiology of a number of cardiovascular diseases including hypertension, CAD and heart failure (97). Van Guilder et al. (98) demonstrated that endothelin-1 mediated vasoconstrictor tone also increases with age in healthy men, but can be alleviated with regular aerobic exercise. This suggests that in older and diseased populations both increased endothelin-1 levels together with decreased NO bioavailability may be responsible for the increased vascular tone (98,99). The sympathetic nervous system may also influence on vasoconstriction, at least in elderly. This was demonstrated by Thijssen et al. (100) who showed that older men had an impaired FMD response of the superficial femoral artery, which increased by local blunting of the sympathetic responsiveness, but remained unaltered during sympathetic activation. Wray et al. (101) suggest that an elevated angiotensin II type 1 receptor sensitivity in healthy, older adults at rest may be particularly relevant to the progression of cardiovascular disease states, characterised by an elevation in both sympathetic nerve activity and angiotensin II. Exogenous angiotensin II-mediated vasoconstriction was however greatly reduced during isolated, small muscle mass exercise, indicating that exercise may play a role in counteracting the reduced vascular conductance with age.

### Endothelial dysfunction

Endothelial dysfunction occurs when the balance between vasoconstriction and vasodilatation is disturbed, causing damage to the arterial wall. Endothelial dysfunction is considered an early marker for atherosclerosis, preceding angiographic and ultrasonic evidence of atherosclerotic plaque (93) and may be present already in childhood (102). The vasomotor function of coronary and peripheral arteries depends on the interplay between eNOS-derived NO-production and NO-degradation by reactive oxygen species (ROS) (103,104). Under normal circumstances, ROS are produced in small amounts by a variety of enzymes and function primarily as signal molecules. In patients with CAD or with elevated risk factors, ROS are however produced in excessive amounts and has been shown to inactivate NO production. This may ultimately exhaust the protective effect of the endogenous, anti-inflammatory systems within the endothelial cells. As a consequence, the endothelium becomes not only dysfunctional, but the cells may also lose integrity, progress to senescence, and detach into the circulation (105). Emerging evidence suggests that a subset of bone marrow-derived endothelial stem cells, so-called endothelial progenitor cells (EPCs), can mobilize to the injury site and complement repair afforded by pre-existing endothelium (106). Hill et al. (107) showed that the degree of endothelial dysfunction correlated inversely with the number of EPCs, indicating that a possible mechanism for endothelial dysfunction may be caused by a relative deficiency of EPCs.

### Endothelial function assessment

Endothelial function can be assessed invasively using acetylcholine, which acts via musacrinic membrane receptors to mediate release of NO. The endothelium-dependent vasodilator response may serve as a surrogate for the bioavailability of NO, and in healthy arteries endothelium-dependent dilatation predominates while in the presence of endothelial damage, vasoconstriction predominates (88,93). Also, infusion of other dilating compounds such as serotonin, bradykinin, adenosine and substance P have been used to provoke coronary or peripheral artery dilatation to be quantified by forearm plethysmography, coronary angiography or positron emission tomography (108).

### Ultrasound assessment of FMD of the brachial artery

The most widely used technique today for detecting endothelial dysfunction is noninvasively high-resolution ultrasound to assess brachial artery diameter dilatation (105,109). This test is considered the prime standard for clinical research on conduit artery endothelial biology (105). The brachial artery diameter is measured at baseline and after reactive hyperaemia produced by 5 minutes of upper or lower arm occlusion (102,110). The reactive hyperaemia induces increased blood flow and shear stress, stimulating NO-release and flow-mediated dilatation (FMD) that can be quantified as an index of endothelial function (110). Also prostacyclin, endothelin-1 and EDHF may be released by the endothelium in response to shear stress (99,111). A small FMD-response to elevated shear stress is interpreted as indicating endothelial dysfunction and an associated increased risk of cardiovascular disease. This was demonstrated by Lieberman et al. (112) who found FMD of the brachial artery to be reduced in relatively young patients with CAD compared to healthy individuals.

### Relation between coronary and peripheral endothelial function

The systemic nature of endothelial dysfunction is reflected by a relation between coronary artery endothelium-dependent vasomotor responses to acetylcholine and the assessment of FMD induced by reactive hyperaemia in the brachial artery. Anderson et al. (113) observed a significant, but relatively low correlation ($r = 0.36$) between FMD in coronary and brachial arteries. Takase et al. (114) studied the relation between the two techniques and obtained a much stronger correlation ($r = 0.78$) when adjusting for initial differences in diameter and flow ratio. Other studies have concluded that impairment of FMD in the brachial artery is closely related to both angiographic and myocardial perfusion imaging evidence of CAD (115,116). Thus, these data suggest that the noninvasive assessment of FMD in brachial arteries could be used as a surrogate measure for coronary artery endothelial function.

### Prognostic impact of endothelial dysfunction

Several studies in healthy individuals have shown a correlation between endothelial dysfunction and the presence of cardiovascular risk factors such as hypercholesterolemia, hypertension, smoking, diabetes and a positive family history

of premature CAD (117-121). The total number of risk factors has been found to be a potent predictor of endothelial dysfunction as measured both by the acetylcholine test in coronary arteries (118) and by the brachial artery ultrasound FMD test (121). Celermajer et al. (121) studied the superficial femoral and brachial artery in 500 clinically well, non-hypertensive subjects. The results showed that reduced flow-mediated dilatation was significantly related to hypercholesterolemia, cigarette smoking, higher blood pressure, male gender, older age, family history of premature vascular disease and larger blood vessel size. The authors concluded that loss of endothelium-dependent dilatation in the systemic arteries is associated with interaction of the same risk factors known to predispose to atherosclerosis and its complications later in life.

Impaired coronary and brachial artery endothelial function predicts both long-term and short-term atherosclerotic disease progression and cardiovascular event rates including death (122,123). Schashinger et al. (124) found that impaired coronary artery vasodilator reactivity was associated with long-term atherosclerotic disease progression and cardiovascular event rates over 7.7 years follow-up. The coronary vasoreactivity showed to be a significant predictor of poor prognosis, even after adjustments for traditional risk factors or the presence of atherosclerosis. In the largest such study to date involving 308 patients, both epicardial and microvascular coronary endothelial dysfunction independently predicted acute cardiovascular events in patients with and without CAD over 3.8 year follow-up (125).

Like in the coronary arteries, impaired FMD measured by ultrasound in the brachial artery has also been found to be a predictor of future cardiac events. This was demonstrated in a study by Neunteufl et al. (126) who found that patients with chest pain and no angiographic evidence of CAD, heart failure or valvular defects, which showed impaired brachial artery FMD, were more likely to undergo PCI and coronary artery bypass surgery than patients with normal FMD during five years follow-up. In addition, Patti et al. (127) found that impaired FMD also predicted the occurrence of in-stent restenosis in patients undergoing PCI. Gokce et al. (128) examined brachial artery FMD in 199 patients with peripheral arterial disease 14 months after elective vascular surgery. The results showed that impaired endothelial function independently predicts long-term cardiovascular events in this patient group, and that

noninvasive assessment of endothelial function using brachial artery FMD may serve as a surrogate end point for cardiovascular risk. Modena et al. (129) studied brachial artery FMD in post-menopausal women with newly diagnosed hypertension, and concluded that patients had increased risk over the next five years when endothelial function was not reversed by six months of antihypertensive therapy. Thus, endothelial dysfunction acts as a marker for patients with “preclinical” vascular disease and identifies patients in whom therapeutic intervention may be beneficial.

Even if the predictive value of brachial artery FMD for cardiovascular events is shown in several studies (126-133), it is not unambiguous established (134,135). A meta-analysis by Witte et al. (136) found that the relation between brachial artery FMD and cardiovascular risk factors was affected by the baseline cardiovascular risk. Their results indicated that only in patients with low risk, brachial FMD is related to the principal cardiovascular risk factors and to an estimated 10 years risk of CAD.

**Effects of aerobic exercise training on endothelial dysfunction**

Strategies that reverse endothelial dysfunction have important clinical applications in a variety of CVD states. Studies have shown that various interventions improve endothelial function including lipid-lowering therapy, antioxidant therapy, inhibition of angiotensin-converting enzyme or angiotensin II receptor blockade, smoking cessation, dietary interventions, and physical exercise (137-139). Aerobic exercise increases blood flow to the exercised limbs and myocardium, and the increased blood flow augment shear stress, which in the presence of normal endothelial function produces vasodilatation (111,140). The increased shear stress promotes vasodilatation by increasing the vascular expression of eNOS and thereby enhancing the release of NO (141,142). The preservation of endothelial integrity depends on the balance between injury and the endogenous capacity for repair, and the restoration of the equilibrium between NO production and inactivation by ROS appears to be a primary mechanism contributing to the exercise-mediated improvements of endothelial function (103). Circulating EPCs derived from the bone marrow also seem to play a key role in contributing to enhanced tissue perfusion (103), since EPCs are found to increase both after regular (143) and acute (144) exercise, increasing both FMD and vascular endothelial growth factor (VEGF). Indeed, Sandri et al. (145) demonstrated that repetitive episodes of ischemia during exercise training was

required to induce a sustained elevation of plasma VEGF concentrations and EPC counts in patients with peripheral artery occlusive disease. Also prostacyclin and EDHF contribute to exercise hyperaemia in humans, however in a more limited role (92,99,146). Together, all these substances have been shown to inhibit multiple processes involved in atherogenesis and to promote health (93).

**Systemic effects of exercise**

It has been demonstrated that beneficial effects of exercise are not only confined to the trained extremity, but also induces a systemic effect on endothelial function (40,147). Regular aerobic exercise is thus an important non-pharmacological option to delay the decrease in endothelial function associated with ageing and has been found to reverse impaired endothelial function in individuals with atherosclerosis, hypertension, dyslipidaemia, type 2 diabetes and heart failure (148-154). However, a recent analysis of 27 000 subjects reported that differences in risk factors explained 59% or less of the cardiovascular risk reduction with exercise (155). This indicate that direct systemic shear stress mediated effects on the endothelium also contribute to the reduction in cardiovascular events associated with large muscle-mass exercise training, since improvements in conduit and resistance vessel endothelial function are found to occur independent of changes in cardiovascular risk factors (156). Exercise thus seems to exert direct effects on the vasculature via the impact of repetitive increases in shear stress on the endothelium, which transduce functional and structural adaptations that decreases cardiovascular risk (157).

The beneficial effect of exercise on the endothelium was clearly demonstrated by Hambrecht et al. (158), who found that in patients with stable CAD and an angiographically documented stenosis amenable for PCI, a 12 months exercise training program resulted in a higher event-free survival rate than with standard PCI intervention. Interestingly, both PCI and exercise training were equally effective in improving symptom-free exercise tolerance. However, the exercise intervention was associated with higher exercise capacity and $VO_{2max}$ after 12 months than in the PCI group. In addition, the training intervention was found to be significantly more cost-effective. The benefit of regular training was maintained at two years with a markedly better improvement of exercise capacity and better event-free survival in the training group (159). Moreover, our research group (40) demonstrated a systemic improved

effect on FMD measured in the brachial artery after 12 weeks of aerobic treadmill exercise in heart failure patients (Figure 2). The observed improvement was greater after high-intensity aerobic exercise compared to moderate intensity, and there was also a close relationship between improved aerobic capacity and improved FMD (r = 0.69).

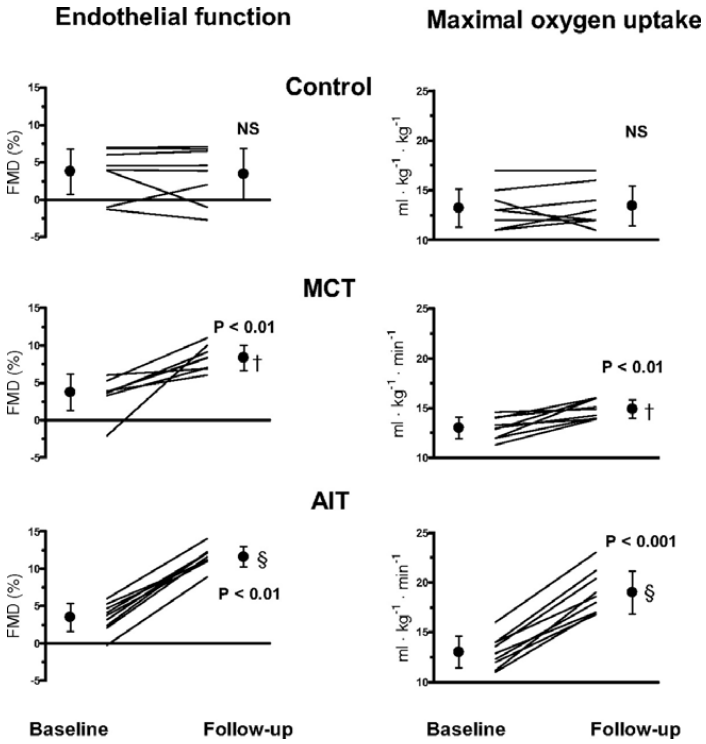


**Figure 2.** Left, Endothelial function measured as FMD. Right, Maximal oxygen uptake. Data are mean±SD. Lines represent individual values. Probability values inside figures indicate within-group differences. § Aerobic interval training (AIT) different from control and moderate continuous training (MCT), *P*<0.01; † different from control, *P*<0.01. Reprinted from Wisløff et al. *Circulation* 2007;115:3086-94.

### Athletes arteries

Highly endurance-trained individuals are associated with increased arterial diameter compared to untrained (160). The size and blood flow of the proximal limb arteries thus seem to be adjusted to the metabolic needs of the corresponding extremity musculature. This emphasise the impact of exercise training or disuse on the structure and the function of the arterial system. Although evidence exists that aerobic exercise gives improved endothelial function when it is impaired (104,138,140), the influence in young healthy individuals and athletes is however less clear. It has previously been reported that exercise may enhance, decrease or have no effect on endothelial function in young, healthy individuals (161-163). Two studies have also suggested that high-intensity exercise may induce oxidative stress that may adversely affect endothelial function (162,164).

### Effective exercise

The question whether high-intensity exercise outmanoeuvres the possible adverse effects both in healthy individuals and in patients at cardiovascular risk remains to be further clarified. As aerobic exercise capacity seems to reflect a continuum between health and cardiovascular disease and death, it is important to design effective training programmes that effectively contribute to promote health. As consensus about the most efficient exercise mode to improve health is lacking, the effect of aerobic exercise at different intensities needs to be further elucidated.

## AIMS OF THE STUDY

The main purpose of the study presented in this thesis was to study cardiovascular adaptation to aerobic exercise of either high- or moderate intensity, in trained and untrained young persons, in CAD-patients, and in individuals with the metabolic syndrome. More specific, we wanted to determine what exercise intensity is the most effective for increasing aerobic capacity in CAD-patients and for reducing the cardiovascular risk factors in individuals with the metabolic syndrome. We also wanted to evaluate how endothelial function is affected by both acute and chronic exercise among individuals with different aerobic capacity and cardiovascular risk. The specific aims were:

I. To determine if high- or moderate exercise intensity is most effective for increasing $VO_{2max}$ in CAD-patients. We hypothesised that interval exercise at high intensity is superior to continuous exercise at moderate intensity for increasing $VO_{2max}$.

II. To evaluate brachial artery FMD and diameter in highly endurance-trained females compared to untrained females. We hypothesised that endothelial function is well preserved among sedentary, healthy females and that a high training status will not improve the dilating capacity any further.

III. To evaluate the influence of high vs. normal aerobic capacity and a single bout of interval exercise at high intensity on arterial diameter, peak blood flow, brachial artery FMD, bioavailability of NO, and antioxidant status in well-trained and untrained young men. We hypothesised that athletes would have larger arterial diameter but similar endothelial function compared to untrained, and that one high intensity exercise session would not impair endothelial function in either group.

IV. To determine the optimal level of exercise intensity needed to treat the metabolic syndrome and its associated cardiovascular abnormalities. We hypothesised that high intensity exercise is more effective than continuous moderate exercise to reverse features of the metabolic syndrome.

# MATERIALS AND METHODS

## Subjects

### Study I

Twenty-one participants with angiographically documented CAD in at least one major epicardial vessel were enrolled in the study. In addition, subjects had clinical evidence of CAD in form of previous myocardial infarction, significant stenosis treated with coronary artery bypass graft surgery (CABG) or percutaneous coronary intervention (PCI), or ischemia in exercise-ECG. Eleven patients were randomly assigned to high-intensity exercise and 10 to moderate intensity exercise. Exclusion criteria were left main coronary artery disease, unstable angina pectoris, intermittent claudication, myocardial infarction within the last three months, CABG or PCI performed within the last 12 months, complex ventricular arrhythmias, left ventricular ejection fraction below 40%, orthopaedic or neurological limitations to exercise, or regular exercise for the past three months.

### Study II

Sixteen endurance-trained females and 14 females with no habit of exercise were recruited among university students. The athletes were cross-country skiers, track and field- or orienteering runners, and were recruited if they exercised regularly for a minimum of three times per week. None of the subjects were smokers, frequently passive smokers, pregnant or taking cardiovascular- or antioxidant medication. Subjects who had a history of diabetes, dyslipidaemia, hypertension, thyroid illness, or a family history of premature cardiovascular disease were excluded. Six of the endurance-trained and seven of the sedentary women were taking oral contraception.

### Study III

Ten highly endurance-trained male athletes (cross-country skiers, orienteering runners and biathlon skiers), all in the national team in their respective sport and within top ten on a national basis, and seven healthy sedentary males recruited among university students took part in the study. Inclusion criteria were a $VO_{2max}$ either above 70 mL · $kg^{-1}$ · $min^{-1}$ for athletes or below 55 mL · $kg^{-1}$ · $min^{-1}$ and less than one hour of exercise training per week for controls. Exclusion criteria were

history of hypertension, diabetes mellitus and family history of premature cardiovascular disease.

**Study IV**

Twenty-eight patients with metabolic syndrome defined according to the WHO-criteria (74) took part in the study. Patients were randomised and stratified according to age and gender into a interval training group, a moderate training group or to a control group. Exclusion criteria were unstable angina, recent coronary arrest (within four weeks), heart failure, severe pulmonary disease, uncontrolled hypertension, kidney failure, orthopaedic and/or neurologic limitations, cardiomyopathy, pregnancy, drug or alcohol addictions, and participation in parallel studies.

## Testing procedures

### Testing of $VO_{2max}$

All tests of $VO_{2max}$ were accomplished during uphill treadmill walking or running since this also was the exercise training mode. Uphill treadmill exercise offers advantage when training and testing humans since it recruits a larger muscle mass and a slower cadence, producing the highest oxygen uptake (29).

*CAD and metabolic syndrome patients (study I and IV)*

For CAD and metabolic syndrome patients, all $VO_{2max}$-tests were accomplished using MetaMax II portable system (Cortex, Leipzig, Germany). To familiarise with treadmill walking, the $VO_2$-test started on a flat treadmill learning to walk without grasping the handrails. As soon as the patients were walking properly, the speed and inclination were individually adjusted for a 10 minute warm-up. After the warm-up period, the $VO_{2max}$-test was completed using an individually adjusted ramp protocol increasing both treadmill speed and inclination. For CAD-patients a standard 12-lead ECG was recorded at rest and at the end of each work level. The intention of the individually adjusted protocol was to bring the subjects to $VO_{2max}$ after approximately 8-12 minutes (165). The average of the three highest 10 seconds measurements was determined $VO_{2max}$. Heart rate was continuously recorded using Polar Sport Tester (Polar Electro OY, Finland) and maximum heart rate ($HR_{max}$) was determined.

*Considerations of $VO_{2max}$-measurements in CAD-patients (study I)*

To ensure that exercise is conducted at the proper intensity, it is important that patients are exercising to their maximal effort on the initial $VO_{2max}$-test. If not, the reported exercise intensities are likely underestimates of the actual ranges. A plateau of oxygen uptake despite increased work load and a respiratory exchange ratio (RER) above 1.05 were used as criteria for reaching the true $VO_{2max}$ (29). For the CAD-patients a plateau of the $VO_2$-curve was not uniformly seen at pre-test, even if the effort was close to exhaustion (RER = 1.09). The determination $VO_{2peak}$ was thus used in paper I but the term $VO_{2max}$ is uniformly used throughout this thesis to simplify the expression of maximal aerobic capacity. Also, to secure that learning to walk properly on the treadmill was not influencing the $VO_{2max}$-measurements, an instructor blinded for the values of the initial test carried out a second $VO_{2max}$-test within one week on 10 of the CAD-patients. The coefficient of variation between the two measurements was only 0.5%, certifying that a true $VO_{2max}$ was measured initially (unpublished results).

*Healthy individuals (study II and III)*

An individually adjusted treadmill running ramp protocol was used for measuring $VO_{2max}$ in healthy individuals using MetaMax II. After a 10 minute warm-up period at a speed (7-10 km $\cdot$ $h^{-1}$) and an inclination (0-5%) adjusted to the subject's fitness level, the inclination was increased to 10%. The speed was thereafter increased by 1 km $\cdot$ $h^{-1}$ every minute until exhaustion. To ensure that a true $VO_{2max}$ was reached, two criteria had to be met: A levelling-off of $VO_2$ despite an increase of exercise power and a respiratory exchange ratio above 1.05.

**Brachial artery FMD**

*Method used in study II-IV*

Endothelium-dependent and independent dilatation was studied according to the method originally described by Celermajer et al. (102). The guideline for determination of FMD described by Corretti et al. (110) was followed. Endothelial function of the artery was measured using high resolution vascular ultrasound (14 MHz linear-phased array probe, Vivid 7 system, GE Vingmed Ultrasound AS, Horten, Norway). The measurements were performed on the left brachial artery above the

antecubital fossa. After a ten minutes rest in supine position in a quiet, air-conditioned room with a stable temperature of 22 ± 1°C, blood flow (with an insonation angle at 60°) and internal diameter of the brachial artery was assessed. Thereafter we inflated a pneumatic cuff (Hokanson SC10) on the upper arm to 250 mmHg for five minutes and deflated it to create an ischemia-induced hyperaemic elevated blood flow. Data were recorded 10 seconds after cuff-release to measure peak blood flow and thereafter every 30 seconds for five minutes observing the artery diameter. The subjects then rested until the baseline diameter was restored (5-10 minutes) before endothelium-independent response was studied. After sublingual administration of 500 µg glycerol trinitrate (GTN) the diameter of the artery was measured for four minutes. All ultrasound images were analyzed in random order, using EchoPAC (GE Vingmed Ultrasound AS, Horten, Norway) by one person not knowing the group allocation of the subjects. To avoid confounding effects of arterial compliance and cyclic changes in arterial dimension all measurements were obtained at the peak of the R-wave in the ECG. Diameters were measured from intima to intima using callipers with a 0.1 mm resolution. The mean of three (study II and IV) and five (study III) diameter measurements and flow measurements were used in the calculation of FMD, GTN and flow-responses. Maximal dilatation was observed one minute after cuff release in all studies and those data are presented in the results.

*Methodological considerations*

We applied the FMD test of the brachial artery induced by reactive hyperaemia because this test may represent the prime standard for clinical research on conduit artery endothelial biology (105). The test is widely used, but many between-laboratory differences in methodology have made between-study comparisons challenging (136,166). Therefore, some methodological considerations regarding the execution must be made.

*Cuff placement*

A cuff placement proximal to the measure site was chosen to produce a larger brachial artery dilatory response (167), which is favourable to detect any further dilatation after the expected large post-exercise resting arterial diameter resulting from an acute exercise bout. In addition, studies showing relation between FMD in coronary and brachial arteries in suspected coronary artery disease have used both

proximal and distal cuff placement to create a hyperaemic stimulus (113,114). The studies in this thesis were conducted in 2004, and the guidelines by Corretti et al. (110) published in 2002 were followed. The Corretti report presented state-of-the-art information in the area of reactive hyperaemia mediated FMD of the brachial artery assessed by ultrasound, but there was no consensus whether upper arm or forearm occlusion provided the most accurate information.

*NO-dependency*

Two "updates" of the guidelines presented in 2005 (99,108) stressed the importance of distal occlusion when the intention is to measure NO-mediated endothelial vasodilatation. At present, the consensus seem to be that dilatation is blocked by the NO inhibitors L-NMMA or L-NAME when the occlusion is of five minutes duration, performed with no handgrip exercise and the cuff is placed distal to the measure site (141,168-171).

*Significance of cuff placement*

An important methodological aspect is therefore that when the mechanistic isolation of NO is desirable, distal occlusion should be used, but when other clinical or basic research perspective is desirable, proximal occlusion should not be refused (99). A study by Silva et al. (172) concluded that the cuff location during FMD measurements does not play an important role in the accuracy of the test to differentiate patients with and without CVD risk factors. It should also be stressed that the extent of studies finding a predictive value of brachial artery FMD and the occurrence of mortality and cardiovascular events have used both proximal (123,126-128,130,132,173) and distal cuff placement (129,131,133,174). This indicates that mechanisms independent of NO also contribute (e.g. Prostacyclin, EDHF, potassium, and sympathetic activation) to cardiovascular health and their relative contribution should be clarified (175). Both upper and lower arm cuff placements should therefore be used in future research to detect in what extent NO-mediated or non-NO-mediated mechanisms contribute to different treatments of cardiovascular diseases.

*Stimulus-response*

Arterial wall shear stress during peak hyperaemia has been found to be linearly related to the resulting diameter percent change from baseline (176). This makes a

challenge in study II and III where the size of the brachial artery differs between groups. Shear rate was used as a surrogate measure for vascular shear stress, and was calculated as blood flow velocity ($cm \cdot s^{-1}$) divided by diameter (cm) (99). The adjustment to shear rate area under curve was not used because there was no clear evidence as to which shear stimulus quantity normalisation would be presented until recently (177).

*Repeatability*

The reproducibility and repeatability of the method have been described previously (99,108) and the coefficient of variation of intraobserver baseline brachial diameter measurements in our laboratory is 2.9% (178).

*Anthropometrical considerations*

In study III, we compared highly trained athletes with untrained counterparts, and the athletes had significantly less body weight than untrained. When comparing people with different body weight in running, $VO_{2max}$ should be expressed relative to body weight raised to the power of 0.75 (179) because $VO_2$ does not increase in direct proportion to body weight. Data are thus also presented as $mL \cdot kg^{-0.75} \cdot min^{-1}$. In addition, blood vessel diameter and FMD were also corrected and analysed relative to body surface area (BSA) (180).

## Aerobic exercise training

The high-intensity exercise was chosen to be aerobic interval exercise at 80-90% of $VO_{2max}$ because this training method has been employed by our research group in healthy individuals earlier, being effective in improving $VO_{2max}$ at a relative short time-period (24,181). The moderate intensity exercise at 50-60% of $VO_{2max}$ was selected because it is typically used in training studies involving patients with CAD (64) or with the metabolic syndrome (78).

**CAD-patient training (study I)**

All CAD-patient training consisted of uphill treadmill walking three times per week for ten weeks. The high intensity interval group carried out a 5 minutes warm-up period at an intensity corresponding to 50-60% of $VO_{2max}$ (65-75% of $HR_{max}$) (29,182) before walking four intervals of 4 minutes at 80-90% of $VO_{2max}$ (85-95% of $HR_{max}$). Between

the intervals 3 minutes walking at 50-60% of $VO_{2max}$ was conducted. The training session was terminated by a 3 minutes cool-down period at 50-60% of $VO_{2max}$. This gave a total exercise time for the high intensity group of 33 minutes. To equalise the total work performed by the two groups the following calculation was used: the average $VO_{2max}$ for all subjects before training was 2.55 L · $min^{-1}$. The high intensity group performed 4 x 4 minutes exercise at 2.29 L · $min^{-1}$ (90% of $VO_{2max}$) and 3 x 3 minutes exercise at 1.53 L · $min^{-1}$ (60% of $VO_{2max}$). The total $VO_2$-time relationship for the high intensity group was then divided by the intensity for the moderate intensity group (50.49/1.53 = 33 minutes). Finally the warm-up and cool-down exercise time for the high intensity group (5 + 3 minutes) at 1.53 L · $min^{-1}$ was added to this value. The moderate intensity exercise training thus consisted of 41 minutes continuous exercise at an intensity of 50-60% of $VO_{2max}$, representing the same total training load as the high intensity aerobic exercise group.

**Metabolic syndrome training (study IV)**

Both exercise-groups performed aerobic endurance training, walking/running uphill on a treadmill three times per week for 16 weeks. The high intensity interval group warmed-up for 10 minutes at 70% of $HR_{max}$ before performing four 4 minutes intervals at 90-95% of $HR_{max}$, with 3 minutes active recovery at 70% of $HR_{max}$ between each interval, and a 5 minutes cool-down period, giving a total of 40 minutes. To equalise training volume (i.e. spending the same amount of kcal each session) the moderate intensity exercise group had to perform 47 minutes at 70% of $HR_{max}$ each exercise session (see above section for calculation). The control group followed advice from their family doctor. For assessment of the acute effects of exercise, the patients accomplished one session of their respectively training regime.

**Adjustment and control of training**

All subjects exercised using a heart rate monitoring device during every training session to control their corresponding exercise heart rate relative to $VO_{2max}$, and was encouraged by the instructor to exercise as close to the upper intensity border as possible. The speed and inclination of the treadmill were continually adjusted along as training adaptations occurred, to ensure that all training sessions were carried out at the desired heart rate throughout the training period. The BORG 6-20 scale (183) was used to measure the rate of perceived exertion after each training session.

**Athlete and healthy individual acute exercise (study III)**

In study III, highly endurance trained men and their untrained counterparts accomplished one high-intensity aerobic exercise session. Subjects were not allowed to exercise for the last 48 hours before the study started. In addition, the athletes did not perform any hard bouts of exercise-training the last 96 hours prior to the experiment. Immediately after the initial FMD measurements, all subjects performed a treadmill exercise protocol at the same relative exercise intensity: After 15 minutes warm-up, running at 60-70 % of $HR_{max}$, subjects ran 5 x 5 minutes with the three last minutes of every bout above 90 % of $HR_{max}$. The two first minutes of the bout were used to gradually enter the training zone. Between each interval, subjects performed two minutes active recovery at an intensity corresponding to 60-70 % of $HR_{max}$.

## SUMMARY OF RESULTS

**Paper I. High intensity aerobic interval exercise is superior to moderate intensity exercise for increasing aerobic capacity in patients with coronary artery disease.**

1. The 18% improvement of $VO_{2max}$ after aerobic interval training was significantly greater than the 8% improvement after moderate intensity exercise training.
2. Aerobic interval training improved $VO_{2max}$ by 0.63% per training session attended, which was more than twice as high compared to the 0.29% improvement in the moderate intensity group.
3. There were no detectable changes in resting blood pressure, resting heart rate, or body mass in neither group after the training period.
4. There were no cardiac events during the study.

**Paper II. Endothelial function in highly endurance-trained and sedentary, healthy young women.**

1. Despite a 50% difference in $VO_{2max}$, there was no difference in brachial artery FMD between the sedentary and the trained group.
2. The endurance-trained group showed a FMD of 14.8% compared to 16.4% in the untrained group.
3. There was a trend towards larger absolute baseline arterial diameters in the trained group, and when adjusting for body surface area, the trained females showed a 9% larger baseline diameter than their sedentary counterparts.

**Paper III. Endothelial function in highly endurance-trained men: Effects of acute exercise.**

1. There were no differences in FMD between groups, neither expressed in absolute terms nor in percent, at any time-point, even when normalised for shear stress.
2. Resting as well as maximal arterial diameter measured one minute after cuff-release were 10-15% larger in the trained group both before exercise, one hour, 24 hours and 48 hours after the exercise session.

3. Nitric oxide bioactivity was elevated by 93% in the trained group and by 63% in the untrained group one hour after the training, and decreased to baseline level after 24 hours in the sedentary group, but stayed elevated by 80% above baseline after 24 hours and by 93% after 48 hours in the trained group.
4. The circulating antioxidant level increased by 7% and 10% one hour post-exercise in the untrained- and trained group respectively. The antioxidant status was back to baseline 24 hours after exercise in both groups and decreased to a level 5% below baseline in the trained group after 48 hours.

**Paper IV. Aerobic interval training vs. continuous moderate exercise as a treatment for the metabolic syndrome - "A Pilot Study".**

1. Aerobic interval training and continuous moderate exercise training increased $VO_{2max}$ by 35% and 16%, respectively after 16 weeks of exercise.
2. Aerobic interval training and continuous moderate exercise improved FMD by 9% and 5%, respectively.
3. Both groups exhibited a slight reduction (3-4%) in body weight despite no diet alterations during the intervention period.
4. A decreased systolic and diastolic blood pressures was seen in both groups (~10 mmHg, and ~6 mmHg, respectively).
5. At the end of the training period, 46% in the aerobic interval training group and 37% in the continuous moderate exercise group were no longer diagnosed with the metabolic syndrome, as opposed to the control group in which the syndrome persisted in all subjects.

## DISCUSSION

The results of the present thesis demonstrate that high-intensity aerobic exercise is superior to moderate intensity exercise for increasing aerobic capacity in both patients with CAD and the metabolic syndrome. Endurance-trained athletes showed similar FMD but larger arterial diameter than untrained, and possessed an increased bioavailability of NO and elevated antioxidant status to acute high-intensity exercise. Furthermore, aerobic exercise, at high intensity in particular, seems to be an important factor for improving the risk factors of the metabolic syndrome, including endothelial dysfunction. Because of the equalisation of training-load this solely point out high exercise intensity as a key factor for increasing $VO_{2max}$ and decreasing cardiovascular risk factors among these patients.

### Aerobic exercise in CAD-patients (study I)

The main goal of study I was to evaluate the effect of exercise in CAD-patients when intensity is the only parameter being manipulated. The improvement of 18% in the high intensity group compared to 8% in the moderate intensity group reflects the importance of exercise intensity for increasing $VO_{2max}$. This may have important impact not only on functional capacity but also on survival prospects as improved aerobic capacity has been shown to reduce mortality (47-53).

#### Effects of exercise intensity for improving $VO_{2max}$

While our study I is one of very few where CAD-patients were performing aerobic interval exercise at 80-90% of $VO_{2max}$, continuous exercise at 50-60% of $VO_{2max}$ is more frequently used (64). Two earlier studies involving CAD-patients have employed aerobic interval exercise with elements of the same high intensity as in the present study, showing the largest improvement of $VO_{2max}$ to date (43,184). The improvement in $VO_{2max}$ of 37-42% found in these studies are however difficult to compare to our study because of the longer training period of 12 months. Jensen et al. (185) had two groups of CAD-patients training for 12 months, involving high-intensity exercise within the range of the present study. One hundred and eighty-six subjects with a documented CAD event within the previous 24 months were randomised to 45 minutes of walking or jogging at either 85% or 50% of $VO_{2max}$. The results showed that $VO_{2max}$ in the high intensity group increased by 13% which was

significantly higher compared to the 9% increase in the lower intensity group. Adachi et al. (186) compared 29 patients with previous myocardial infarction randomised to either walking exercise at 70% of $VO_{2max}$ or at 55% of $VO_{2max}$ over eight weeks. $VO_{2max}$ increased by 17% in the high intensity group and 9% in the moderate intensity group. Contrary to these studies, Blumenthal et al. (187) did not detect differences between moderate intensity (75% of $VO_{2max}$) and low intensity exercise (45% of $VO_{2max}$) after 12 weeks of training among 45 patients with myocardial infarction. $VO_{2max}$ increased by 11% within the high intensity group and 14% in the low intensity group, but the differences were not statistically significant. Same conclusions was made by Warburton et al. (188) who found that high-intensity interval training resulted in similar improvements in aerobic fitness in comparison to traditional continuous aerobic exercise training in CAD-patients. In sum, however, these findings support our study with regard to the fact that higher intensity exercise being more suitable for increasing $VO_{2max}$ compared to lower intensity exercise in CAD-patients.

**Equalisation of exercise**

Our results are thus in accordance with previous work indicating that high-intensity exercise is more suitable for increasing $VO_{2max}$ compared to moderate or low intensity exercise (43,184-187). But, in each of the former studies the two groups used the same exercise duration and the higher intensity groups therefore performed a greater total amount of training. It is therefore uncertain whether intensity or total amount of work was the most determining for the increase in $VO_{2max}$. The equalisation of exercise load between the groups in study I was emphasised to control if intensity is a capital factor for increasing $VO_{2max}$. In addition, all subjects exercised with heart rate monitoring device and the load of the treadmill could therefore progressively be adjusted to keep the relative exercise intensity constant as training adaptations occurred throughout the study. More recent work from our research group have confirmed the results from study I in healthy individuals (189), and in patients with chronic heart failure (40), intermittent claudication (190) and metabolic syndrome (study IV).

### Absolute vs. relative improvement of $VO_{2max}$

The initial $VO_{2max}$ of the patients in our study was 32.0 mL · $kg^{-1}$ · $min^{-1}$, which is higher compared to the other studies evaluating exercise intensity in CAD-patients (18.7-25.3 mL · $kg^{-1}$ · $min^{-1}$) (185-187). Thus, the 18% improvement of $VO_{2max}$ in the high intensity group is therefore considerable when calculating percentage improvement from such a higher baseline value. In fact, $VO_{2peak}$ increased by 0.63% and 0.29% per training session accomplished for the high and moderate exercise group, respectively.

### Mechanisms of improved $VO_{2max}$

An echocardiographic analysis of the patients in study I, presented by Amundsen et al. in a separate study (39), revealed that left ventricular early diastolic myocardial relaxation rate improved only in the high intensity-exercise group indicating the significance of high intensity for elevation of diastolic function and $VO_{2max}$. This coincides with previous studies where diastolic function seems to be more closely related to $VO_{2max}$ than systolic function (191). A close relationship has previously been found between early diastolic function, stroke volume and $VO_{2max}$ in patients with hypertrophic cardiomyopathy (192). Although not measured it is reasonable to believe that adaptations also appeared in the skeletal muscles due to improvements in oxidative characteristics as well as in endothelial function of the conduit arteries (29,138). Other possible mechanisms of adaptations due to different exercise intensities were therefore further investigated in study II-IV.

## Endothelial function in trained vs. sedentary women (study II)

The results from study II suggest that long-term endurance training does not improve FMD of the brachial artery above normal levels in young, healthy women. Despite a 50% difference in $VO_{2max}$ between the two groups, there was no difference in FMD between highly trained and sedentary individuals.

### FMD in healthy, young individuals

Our results correspond with other cross-sectional comparisons of endothelial function between active and sedentary young subjects. Both longitudinal and cross-sectional studies indicate that exercise training has relatively little or no impact when endothelial function is well preserved at baseline (138,140) while aerobic exercise

interventions have shown improvements in endothelial function when it is reduced by age (193), heart failure (194), CAD (148), hypertension (152) or type 2 diabetes (151). DeSouza et al. (193) reported no differences in forearm vascular responses to acetylcholine between trained and sedentary men aged ~27. Similarly, Taddei et al. (163) reported equal forearm blood flow modifications induced by intrabrachial acetylcholine in male athletes and sedentary subjects aged ~27, and concluded that endothelial function is well preserved and cannot be affected by potentially beneficial intervention such as aerobic exercise. Kingwell et al. (195) found no change in endothelial dilatation in the forearm after four weeks of cycling in 13 sedentary, ~24 year old males. Also, a study by Maiorana et al. (151) found that eight weeks of exercise training did not alter forearm acetylcholine response in middle-aged healthy, sedentary subjects. Contrary, Clarkson et al. (196) found that a 10 week aerobic and anaerobic exercise program improved FMD from 2.2% to 3.9% in male military recruits. This study included smokers, who most likely influenced the results, as smoking is associated with impaired FMD (120). The sum of the discussed studies, together with our results, suggest that aerobic exercise improves endothelial function only when it is impaired at baseline, and that the dilatory response is unaffected by exercise capacity in healthy, young individuals. The phenomenon of improved FMD caused by long-term aerobic training thus seems to be valid mostly when investigations include subjects who possess cardiovascular risk factors or established cardiovascular disease.

**Adjustment for diameter size**

The highly-trained females showed a significantly 9% larger resting brachial arterial diameter when adjusting for BSA. This corresponds to former studies where specifically trained athletes possessed larger conductive arteries compared to untrained counterparts (197,198). One may then speculate if a larger brachial arterial diameter is a stronger indicator of improved endothelial function rather than FMD when comparing highly trained and sedentary young subjects. We found neither any difference in FMD between trained and untrained females when adjusting for BSA. Thus, the results of study II indicate FMD to be similar in highly-trained and sedentary females. This suggests that endothelial function is being well preserved in untrained, though healthy, young women.

## Effects of acute exercise on FMD in healthy individuals (study III)

The main findings of study III was that highly endurance-trained athletes had larger arterial diameter but similar FMD compared to untrained controls, i.e. indicating a long-term exercise induced difference in vessel size. Also, when normalizing for peak hyperaemic shear rate we could not observe any differences in FMD between groups. Furthermore, we observed increased bioavailability of NO and elevated antioxidant status to acute exercise, which was highly dependent upon the time elapsed after exercise.

### FMD before acute exercise

There were no significant differences in FMD between the groups at baseline. This suggests that the FMD, which is believed to be mediated mainly by NO, is well preserved in sedentary young, healthy individuals and not a limiting step for delivering large amounts of blood to the exercising musculature as is the case during strenuous exercise. This indicate that the differences in arterial diameter and not in FMD may be a more important mechanism to accommodate the substantial higher cardiac output that has to be transported by the blood vessels to the exercising muscles in individuals with a $VO_{2max}$ of 75.9 mL · $kg^{-1}$ · $min^{-1}$ observed in the athletes, compared to a $VO_{2max}$ of 47.7 mL · $kg^{-1}$ · $min^{-1}$ in the untrained individuals.

### FMD after acute exercise

FMD measured one hour after the training session was significantly reduced compared to FMD at baseline among the highly endurance-trained athletes, whilst baseline values were observed 24 and 48 hours post-exercise. One may speculate whether this reflects impaired endothelial function one hour after the training session and normalisation within 24 hours. However, we observed increased bioavailability of NO and improved antioxidant status in blood samples taken one hour post-exercise, suggesting that other mechanisms than NO and antioxidant levels were responsible for the transient decay in FMD observed in the endurance athletes. Therefore, the large resting artery diameter observed among the athletes one hour post-exercise combined with high levels of nitric oxide in plasma, may have dilated the vessel close to maximum, reducing the shear stress imposed by reactive hyperaemia and thus reducing FMD.

**Adjustment for shear rate**

Peak blood flow after cuff release was greater in athletes compared to the untrained subjects. Despite the lower absolute peak blood flow, untrained subjects showed higher peak shear rate at all time points compared to the athletes. Silber et al. (176) demonstrated that arterial FMD is linearly proportional to peak hyperaemic shear stress in normal subjects, i.e. the endothelial response is linearly proportional to the stimulus. In line with this, we observed a significant inverse correlation between FMD and resting arterial diameter at baseline ($r = -0.51$) and thus reproduced earlier findings that larger arteries will dilate less compared to smaller arteries (102). The greater FMD-response in small arteries is suggested to be mediated, at least partially, by a greater hyperaemic shear stress. It has been demonstrated that the hyperaemic shear stimulus for FMD is greater in small arteries due to the dependence of postischemic systolic flow on radius squared. Therefore, greater FMD in smaller arteries does not reflect better conduit artery endothelial function (199). Thus, it might be that FMD in the untrained controls, with smaller artery diameter compared to the athletes, was overestimated. However, even when we normalized for shear rate we could not observe any differences in FMD between the groups. The reason for this may be either that the present test of endothelial function is not sensitive enough to detect differences between a normal and a supra-normal endothelial function, or that a supra-normal endothelial function is not necessary to deliver large amounts of blood to exercising muscles. However, due to the significant larger diameter of the brachial artery and a normal FMD the athletes have a substantial higher capacity to transport large amounts of blood during strenuous exercise compared to the untrained individuals, and as such they have improved "functional" arterial function.

**Possible vascular harmful effects of high-intensity exercise**

Study III further detected decreased antioxidant status 48 hours after exercise. It has previously been suggested that high-intensity exercise may induce oxidative stress that impairs the endothelial function (164). Bergholm et al. (162) found that aerobic training (70-80% of $VO_{2max}$) decreased the circulating antioxidant level and impaired the endothelial function in forearm vessels in healthy males after four weeks running training. Their vascular measurements were performed at least 36 hours after the last training session. Accordingly, their data correspond to ours, but in contrast, we found

unchanged FMD and increased NO in blood at both 24 and 48 hours after exercise. The reason for this discrepancy remains unknown but could be related to the much higher level of aerobic capacity in the athletes in the present study yielding other protective endothelial characteristics.

**Significance of increased NO-production**

Interestingly, despite the decreased level of antioxidant capacity (i.e. increased level of reactive oxygen species) 48 hours post acute exercise in athletes, the bioavailability of NO remained 93% above baseline values. This suggests that the transient decrease in antioxidant status in athletes was physiologically insignificant. The increased production of NO may have been responsible for this. Recently, Hambrecht et al. (200) linked the effect of regular exercise training to an increase in eNOS protein expression and activation of eNOS enzyme activity via Akt-dependent phosphorylation at the serine residue 1177 ($Ser^{1177}$). Protein expression of eNOS as well as phosphorylation at $Ser^{1177}$ were found to be two-fold and four-fold higher in the left internal mammary artery after four weeks of exercise training in patients with stable coronary artery disease compared to sedentary counterparts. The $Ser^{1177}$ residue seems to be a target for shear stress sensors, and its phosphorylation leads to a rise in the enzyme activity of eNOS and enhanced NO production (201). Thus, exercise seems to have a dual positive effect by both increased protein expression of eNOS, which may take a few hours (201,202) and it enhances the phosphorylation of eNOS at $Ser^{1177}$ minutes after increased shear stress, thereby leading to increased vascular NO-production. Interestingly, the shear stress-induced phosphorylation of eNOS is maintained (203), whereas the agonist-mediated $Ser^{1177}$ phosphorylation is only transient (204). Hambrecht et al. (200) showed that exercise training has a larger impact upon phosphorylation of eNOS at $Ser^{1177}$ than on the expression of the eNOS protein itself. Sustained phosphorylation of eNOS could thus explain sustained increased NO production in athletes up to at least 48 hours post-exercise. Furthermore, our study showed a sustained increased level of NO for at least 48 hours that occurred in conjunction with reduced levels of blood glucose and low density lipoproteins, both known to be inversely related to the NO-production.

**Significance of blood lipids on FMD**

Low-density lipoprotein cholesterol and triglycerides were significantly higher in the sedentary group while the HDL cholesterol was significantly higher in the trained group. All mean values were still in the normal range. Also in study II we found no difference in FMD between highly trained and sedentary, young women. The endurance-trained women had a higher HDL-cholesterol but similar LDL-cholesterol and triglyceride-values compared to the sedentary group. Similar, Taddei et al. (163) reported the same endothelial function despite higher LDL- and lower HDL-cholesterol in a sedentary group compared to athletes (mean age ~27). This suggests that differences between lipid levels that are still within the normal range do not affect the endothelial function, although it may influence the NO-production in young, healthy subjects on a short term basis. These findings contrast those of Steinberg et al. (205) who found that elevated total- and LDL-cholesterol levels, even in the high normal range, may be associated with endothelial dysfunction. The mean age in Steinberg's study was ~32 years compared to ~24 years in our study. Thus, the endothelial dysfunction may be a long-term effect that is not apparent in early adulthood in non-obese individuals. Kingwell et al. (161) showed improved endothelial function in ~35 year old endurance athletes compared with age-matched sedentary men. A covariance analysis suggested that a lower total cholesterol in the trained group contributed to the enhanced vasodilator response. This supports the hypothesis that total cholesterol level influences the endothelial function more with increasing age. Finally, De Souza et al. (193) reported similar endothelial function and blood lipid profiles in healthy sedentary compared to trained young men.

**Brachial artery diameter size**

Athletes had larger arteries compared to sedentary counterparts, and a large resting brachial artery diameter has been shown to be an independent predictor of CVD events (131,206). However, a larger arterial diameter with preserved function in athletes may be an analogue to physiological hypertrophy of the athlete's heart with improved function vs. the pathological hypertrophy (i.e. observed in patients with heart failure) with impaired function. Increased arterial diameter on the basis of an exaggerated production of nitric oxide in athletes may suggest improved structural function. The mechanisms responsible for mediating vascular structural enlargement are not fully understood but there are indications that NO plays an important part, and

that shear stress is the trigging factor (207). Acute exercise may up-regulate the eNOS expression to buffer increased shear stress. Following long-term exercise training, NO-mediated structural adaptation may occur, resulting in chronic increase in vessel calibre which structurally normalises the shear stress (140). It thus seems that a larger brachial arterial diameter may be a stronger indicator of improved endothelial function rather than FMD, when comparing highly-trained and sedentary young subjects.

The results of study II and III suggest that endothelial function is well preserved in young, healthy males, and that a high aerobic training status due to long term aerobic training does not improve the dilatation capacity any further. However, the transporting capacity of blood is larger in athletes due to a larger artery diameter. In addition, one strenuous high-intensity exercise session increased bioavailability of NO and elevated antioxidant status and did not seem to impair the endothelial function. Large arteries in athletes are most likely linked to good function whereas large arteries in untrained subjects and patients are linked to poor function. Thus, “the athlete’s artery” may be an analogue to the “athlete’s heart” with good function vs. the pathological hypertrophied heart with poor function.

## Role of exercise in reversing the metabolic syndrome (study IV)

The results from study IV indicate that aerobic exercise, and high-intensity exercise in particular, is an important factor for improving aerobic capacity and reversing the risk factors of the metabolic syndrome including endothelial dysfunction, fasting glucose, insulin-action and lipogenesis. The closely supervised training regimens and the comparable training volumes between the two exercise groups are strong features of the study and demonstrate the importance of exercise training in reducing the risks of metabolic syndrome. Exercise training, especially at high-intensity, appears to be highly beneficial in preventing the metabolic syndrome relative to any other currently known interventions. These findings may have important implications for exercise training in rehabilitation programs. While larger studies using exercise with high relative intensity to treat patients with the metabolic syndrome are needed to advance our conclusions, we propose that high-intensity exercise training programs may yield more favourable results than those with low-to-moderate intensities.

**Aerobic capacity**

Of all established risk factors, low aerobic exercise capacity appears to be the strongest predictor of mortality (47-52). Study IV demonstrates that high-intensity exercise increased $VO_{2max}$ to a higher degree than moderate-intensity exercise in patients with the metabolic syndrome. Central oxygen delivery and peripheral oxygen utilisation, probably contributed to the training-induced changes in $VO_{2max}$ (40). Accordingly, high-intensity exercise increased maximal stroke volume (indicated by improved $O_2$ pulse), as well as $Ca^{2+}$ cycling and mitochondrial capacity in skeletal muscle (as assessed by improved SERCA-capacity and PGC-1$\alpha$ levels in m. vastus lateralis) to a larger extent than moderate exercise.

**Aerobic capacity and weight loss**

The similar weight loss between exercise intensities, but a larger total reduction of the cardiovascular risk factors that constitute the metabolic syndrome after high-intensity exercise, are in line with epidemiological observations suggesting that it may be more important to become fit than to loose weight per se (208,209). Moreover, although obesity and aerobic capacity are strong and independent prognostics markers for cardiovascular mortality, the link between aerobic capacity and mortality seems to be stronger (208,209). This suggests that it is more beneficial to target aerobic capacity before weight loss, although improvement of both risk factors probably would be ideal. However, larger studies are needed to address this issue.

**Applicability of high-intensity exercise**

Study IV suggests that exercise in general and high-intensity exercise in particular is partly or fully able to reverse the metabolic syndrome, suggesting that this may be a promising treatment strategy. It is important to create effective and affordable prevention and treatment strategies to improve wide-scale health outcome and slow down the current epidemic of overweight, to prevent the epidemic of metabolic syndrome from reaching global proportions (210). However, despite the results presented here, the interval protocol may not be readily acceptable to the general population of patients with the metabolic syndrome. On the other hand, an exercise intensity of 90% of $HR_{max}$ corresponds to ~20 beats/min below maximum. This implies that the patients would have tolerated higher exercise intensities (but with shorter durations), and that most patients walk “up-hill” on the treadmill to avoid

running and thereby reduce the risk of musculoskeletal injuries caused by the mechanical load at high running speeds. To obtain the intended exercise intensity during home-based interval training, we normally instruct patients to exercise such that they are breathing heavily and talking becomes uncomfortable during each interval, without developing severe leg stiffness, and that it is an absolute requirement that they should be able to perform four-minute intervals in succession. These instructions were satisfactory in old patients with post-infarction heart failure (40) and may therefore also be feasible for patients with the metabolic syndrome. These observations suggest that it may be possible to instruct patients to perform such training without monitoring heart rate.

**Intensity-mediated differences in endothelial function**

High-intensity training improved FMD more than continuous exercise among the metabolic syndrome patients. In keeping with the notion that exercise-induced improvement in vessel relaxation is mainly mediated by NO (211) we observed no group-differences in endothelium-independent relaxation in the brachial artery after administrating nitroglycerine sublingually. This suggests that the effect of high intensity is mediated by improved NO-bioavailability. Consistent with this hypothesis, high intensity, but not moderate intensity, normalised the level of blood glucose, insulin sensitivity and the amount of oxidized LDL-cholesterol, which directly influence NO bioavailability (93). The reason for the difference in FMD between groups is not fully understood, but it seems reasonable to suggest that the low- and high-intensity exercise programs differently affect shear stress on the walls of blood vessels during exercise training, and that this yields differences in molecular responses. Studies performed in humans indicate agreement that NO contributes to resting and post-exercise blood flows, although its contribution during exercise remains controversial (140,212,213). A definitive support for involvement of any specific vasodilator substance is indeed lacking, but numerous vasodilators such as adenosine, ATP, potassium, oxygen, lactate, $H^+$, NO, prostacyclin, and EDHF have been suggested to contribute to the local vasodilatation during the exercise (214). One explanation of exercise-induced improvements of FMD might be a release of one or more of these vasodilator agents from active muscle beds and their subsequent circulation to inactive regions, e.g. the brachial artery.

**Possible systemic endothelial effects during exercise**

Another possible explanation of the improved brachial artery FMD may be through direct stimulation. Even if increased blood flow during exercise is concerned as a muscle task-specific phenomenon, Tanaka et al. (215) found that there was an approximately fourfold increase in blood flow also in the brachial artery from rest to 90% of peak work rate during graded bicycle leg-exercise. Also Green et al. (211) have demonstrated that exercise exerts a generalised effect on the vasculature by increasing NO activity in vascular beds other than those that perfuse the actively working muscles. Their results showed that lower limb exercise actually was a more potent stimulus to forearm shear stress and NO production than localised handgrip exercise, because of an oscillatory pattern of antegrade/retrograde flow in the arm during whole body exercise. In addition to an increased total flow, blood actually flow backwards towards the heart during diastole (216). Such exercise seems to produce both metabolic and haemodynamic stimuli to active and inactive vessel hyperaemia and this flow-pattern may produce a larger shear stress-mediated endothelial NO production than a pulsatile, albeit larger and unidirectional, antegrade flow stimulus (217). This mechanism could therefore, together with reducing CVD risk factors, explain the training-induced improvements in endothelial function in study IV, where FMD was measured in the brachial artery after exercising the legs. This implies that endothelial dysfunction may be systemically improved as soon as a critical muscle mass is trained at a level sufficient to increase blood pressure amplitude and shear stress. It therefore indicates the importance of high-intensity aerobic exercise as a mediator of a sufficient systemic haemodynamic/shear stimulus to induce global adaptation.

**Possible systemic endothelial effects after exercise**

Superior FMD due to high-intensity exercise may also have been mediated by differences in post-exercise shear stress. A recent study by Padilla et al. (218) demonstrated that walking at high intensity elicited the greatest magnitude of brachial artery shear stress during three hours post exercise measurements, compared to moderate and low intensity. The findings demonstrate that the brachial artery continues to be exposed to increases in shear stress during the recovery from walking exercise and that improvement of endothelial function previously observed in training studies may not only be due to the elevated shear stress during exercise but,

also to the alteration during the recovery (218). In view of this study, it is logical to anticipate that our patients training at high intensity would experience the greatest enhancement in brachial artery endothelial function because shear stress is highest in this group also during the hours after exercise. It is however important to keep in mind that improvements in the peripheral blood vessels in our study could also have been mediated through alterations in the sympathetic nervous system or other mechanisms not measured.

**Blood pressure**

Moderate- and high-intensity exercise reduced systolic and diastolic blood pressure by ~10 and 6 mmHg, respectively. Based on a meta-analysis of one million adults, a blood pressure lowering of this magnitude would in the long term be associated with about 40% and 30% decreases in the risks of premature deaths due to stroke and ischemic heart disease, respectively (219).

**Blood parameters**

Furthermore, metabolic syndrome patients exercising at high intensity improved their insulin sensitivity, β-cell function and glucose level more than the group exercising at moderate intensity. All together, study IV suggest that both exercise programs decreased body weight, but high-intensity exercise was particularly beneficial for decreasing fatty acid transport into the adipose tissue and promoting the suppressive effect of insulin on lipogenesis in this tissue. The mechanism for improved insulin action in muscle by high-intensity exercise is not clear. However, exercise is generally known to promote insulin action in muscle by decreasing the intracellular accumulation of triglycerides and promoting fatty acid oxidation (220). Consistently, high-intensity exercise increased mitochondrial biogenesis in skeletal muscle, which is in agreement with recent reports (221,222).

## CONCLUSIONS

The findings of the present thesis demonstrate that high-intensity exercise seems to be superior to moderate intensity for improving aerobic capacity and reduce the risk factors associated with cardiovascular disease, including endothelial dysfunction. The thesis may therefore bring new thoughts into the area of cardiovascular rehabilitation, with respect to the usefulness of high-intensity aerobic exercise for improving cardiovascular health. As improved $VO_{2max}$ is found to be a major determinant of increasing functional capacity and survival, this type of exercise may be employed to optimise the exercise component of both primary and secondary prevention in the future.

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# PAPER II

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# PAPER III

# Endothelial Function in Highly Endurance-Trained Men: Effects of Acute Exercise

Øivind Rognmo, Tor Halvor Bjørnstad, Christian Kahrs, Arnt Erik Tjønna, Anja Bye, Per M. Haram, Tomas Stølen, Stig A. Slørdahl, and Ulrik Wisløff

*Faculty of Medicine and Department of Circulation and Medical Imaging, Norwegian University of Science and Technology, Trondheim, Norway*

## Abstract

Exercise training reverses endothelial dysfunction, but the effect in young, healthy subjects is less clear. We determined the influence of maximal oxygen uptake ($\dot{V}o_2max$) and a single bout of high-intensity exercise on flow-mediated dilatation (FMD), brachial artery diameter, peak blood flow, nitric oxide (NO) bioavailability, and antioxidant status in highly endurance-trained men and their sedentary counterparts. Ten men athletes (mean ± *SEM* age 23.5 ± 0.9 years, height 182.6 ± 2.4 cm, weight 72.5 ± 2.4 kg, $\dot{V}o_2max$ 75.9 ± 0.8 mL·kg$^{-1}$·min$^{-1}$) and seven healthy controls (age 25.4 ± 1.2 years, height 183.9 ± 3.74 cm, weight 92.8 ± 3.9 kg, $\dot{V}o_2max$ 47.7 ± 1.7 mL·kg$^{-1}$·min$^{-1}$) took part in the study. FMD, brachial artery diameter, and peak blood flow were measured using echo-Doppler before, 1 hour, 24 hours, and 48 hours after a single bout of interval running for 5 × 5 minutes at 90% of maximal heart rate. NO bioavailability and antioxidant status in blood were measured at all time points. Maximal arterial diameter and peak flow were 10–15% ($P < 0.02$) and 28–35% ($P < 0.02$) larger, respectively, in athletes vs. controls at all time points, and similar FMD were observed, apart from a transient decay of FMD in athletes 1 hour post exercise. NO bioavailability increased significantly after exercise in both groups and decreased to baseline levels after 24 hours in controls but remained increased 80% and 93% above baseline 24 and 48 hours post exercise in athletes. Antioxidant status was equal in the two groups at baseline and increased by approximately 10% 1 hour post exercise, an effect that lasted for 24 hours. Athletes had larger arterial diameter but similar FMD as untrained subjects, i.e., athletes had larger capacity for blood transport compared with their untrained counterparts. The observed FMD, bioavailability of NO, and antioxidant status in blood were highly dependent on the time elapsed after the exercise session.

**Key Words** flow-mediated dilatation, oxygen uptake, aerobic exercise, athletes

## Introduction

Endothelial dysfunction plays an initial role in the pathogenesis of atherosclerosis (21), and impaired endothelial function has been observed several years before traditional markers of cardiovascular disease (4). Aerobic exercise has previously been found to improve endothelial function in patients with chronic heart failure (16), coronary artery disease (12), hypertension (14), and type 2 diabetes (18) and to prevent age-related endothelial impairment (7). Although it is generally accepted that regular exercise training augments the endothelial function in individuals with impaired function, the effects in young, healthy subjects are less clear. Previous studies conclude that regular exercise may enhance, decrease, or have no effect on endothelial function in healthy subjects (2,5,7). There is only one study of endothelial function in well-trained women athletes (19), with an average maximal oxygen uptake of 60 mL·kg$^{-1}$·min$^{-1}$, reporting larger arterial diameter but similar endothelial-dependent vasodilatation in endurance trained subjects vs. untrained controls. In addition, there are several studies of endothelial function in moderately endurance-trained men (2,7,27), but there are none in highly endurance-trained men athletes. Furthermore, high-intensity endurance training at 70–80% of maximal oxygen uptake has been linked to decreased antioxidant capacity and reduced endothelial function in moderately well-trained men (2), but it is not known whether this is true for highly endurance-trained men.

Thus, in the present study, we compared the influence of high vs. normal aerobic capacity and a single bout of high-intensity interval running on arterial diameter, peak blood flow, endothelium-dependent dilatation in the brachial artery, bioavailability of nitric oxide, and antioxidant status in

Address correspondence to Dr. Ulrik Wisløff, ulrik.wisloff@ntnu.no.

*22(2)/535–542*

*Journal of Strength and Conditioning Research*

well-trained and sedentary healthy men. We hypothesized that athletes would have larger artery diameter but similar endothelial-dependent vasodilatation, and that one high-intensity aerobic exercise session would not impair endothelial function in either group.

## Methods

### Experimental Approach to the Problem

To assess the influence of high vs. normal aerobic capacity and the acute vascular effects of strenuous aerobic exercise, endothelial function was assessed and venous blood samples were taken at baseline, 1 hour, 24 hours, and 48 hours after finishing a single bout of high-intensity interval training (Figure 1). Maximal oxygen uptake ($\dot{V}o_2max$) and maximal heart rate ($HR_{max}$) were measured 1–2 weeks before the study.

### Subjects

Ten highly endurance-trained men athletes (cross-country skiers, orienteering runners, and biathlon skiers) all in the national team in their respective sport and within the top 10 on a national basis, and seven healthy sedentary men recruited from university students took part in the study. Inclusion criteria were a $\dot{V}o_2max$ value either $>70$ mL·kg$^{-1}$·min$^{-1}$ for athletes or $<55$ mL·kg$^{-1}$·min$^{-1}$ and less than 1 hour of exercise training per week for controls. Exclusion criteria were a history of hypertension or diabetes mellitus and family history of premature cardiovascular disease. No subjects were taking any form of medication. Subject characteristics are presented in Table 1. The investigation conforms to the principles outlined in the Helsinki Declaration and was approved by the regional committee for medical research ethics. All subjects who participated in the study provided written, informed consent.

### Training Protocol

To investigate the acute effects of high-intensity aerobic exercise on endothelial function, we chose a high-intensity interval running exercise. Subjects were not allowed to exercise for 48 hours before the study started. In addition, the athletes did not perform any hard bouts of exercise training 96 hours before the experiment. Immediately after the first endothelial function test, all subjects performed a treadmill exercise protocol at the same relative exercise intensity. After a 15-minute warm-up, running at 60–70 % of $HR_{max}$, subjects ran 5 × 5 minutes with the last 3 minutes of every bout >90 % of $HR_{max}$. The first 2 minutes of the bout were used to gradually enter the training zone. Between each interval, subjects performed 2 minutes' active recovery at an intensity corresponding to 60–70 % of $HR_{max}$.

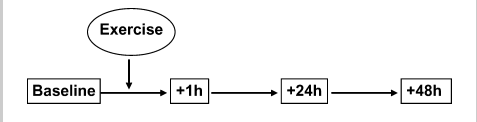


**Figure 1.** Timeline of the experimental protocol indicating when flow-mediated dilatation was measured and when the exercise protocol was performed.

### Endothelial Function

Endothelium-dependent and -independent dilatation was studied according to the method originally described by Celermajer et al. (4). The guidelines for determination of flow-mediated dilatation (FMD) described by Corretti et al. (6) were strictly followed. The reproducibility and repeatability of the method have been established previously (25), and the coefficient of repeatability (3) of baseline brachial diameter measurements in our laboratory is 4%. Endothelial function of the artery was measured using high-resolution vascular ultrasound (14 MHz ultrasound-Doppler probe, Vivid 7 system; GE Vingmed Ultrasound AS, Horten, Norway). The measurements were performed on the brachial artery approximately 4.5 cm above the antecubital fossa. All measurements were performed in the morning after 12 hours' fast. In addition, subjects were not allowed to use nicotine and coffee or any other caffeine-containing beverages for 12 hours preceding testing. All subjects were given instructions not to take vitamins or eat fat-rich meals during the study or to eat 4 hours before testing. After 10 minutes' rest in the supine position in a quiet, air-conditioned room with a stable temperature of 22 ± 1°C, the internal diameter of the brachial artery was assessed. We then inflated a pneumatic cuff on the upper arm to 250 mm Hg for 5 minutes and deflated it to create an ischemia-induced hyperemic elevated blood flow. Data were recorded 10 seconds after cuff release to measure peak blood flow and thereafter every 30 seconds for 5 minutes, while observing the artery diameter. The subjects then rested for 5 minutes until the baseline diameter was restored. Thereafter, endothelium-independent dilatation was measured by administrating 500 μg glycerol trinitrate (GTN) sublingually. To avoid confounding effects of arterial compliance and cyclic changes in arterial dimension, all measurements were obtained at the peak of the R-wave in the electrocardiogram. All ultrasound images were analyzed in random order using EchoPACtm (GE Vingmed Ultrasound AS) by one person who did not know the group allocation of the subjects. Diameters were measured from intima to intima using calipers with a 0.1-mm resolution. The mean of three diameter measurements and flow measurements was used in the calculation of FMD, GTN, and flow responses. Maximal dilatation was observed 1 minute after cuff release in both groups; those data are presented in Results. Shear rate was calculated as blood flow velocity (cm·s$^{-1}$) divided by diameter (cm) (20).

### Exercise Testing

A Metamax portable system (Metamax II; Cortex, Leipzig, Germany) was used for measuring $\dot{V}o_2max$. An individually adjusted treadmill running ramp protocol was used. After a 10-minute warm-up period at a speed (7–10 km·h$^{-1}$) and

**Table 1.** Physical and physiological characteristics of subjects.

| | Trained | Sedentary | *P* value |
|---|---|---|---|
| Age (y) | 23.5 ± 0.9 | 25.4 ± 1.2 | NS |
| Height (cm) | 182.6 ± 2.4 | 183.9 ± 3.7 | NS |
| Weight (cm) | 72.5 ± 2.4 | 92.8 ± 3.9 | <0.001 |
| BMI ($kg \cdot m^{-2}$) | 21.7 ± 0.4 | 27.5 ± 0.9 | <0.001 |
| BSA ($m^2$) | 1.91 ± 0.04 | 2.19 ± 0.06 | <0.001 |
| Resting heart rate ($b \cdot min^{-1}$) | 40 ± 1 | 55 ± 2 | <0.001 |
| Maximal heart rate ($b \cdot min^{-1}$) | 197 ± 2.5 | 203 ± 3 | NS |
| $\dot{V}o_2$max ($mL \cdot kg^{-1} \cdot min^{-1}$) | 75.9 ± 0.8 | 47.7 ± 1.7 | <0.001 |
| ($mL \cdot kg^{-0.75} \cdot min^{-1}$) | 221 ± 2.8 | 151 ± 5.2 | <0.001 |
| Systolic blood pressure (mm Hg) | 122 ± 2 | 128 ± 3 | NS |
| Diastolic blood pressure (mm Hg) | 78 ± 3 | 80 ± 3 | NS |
| Training ($h \cdot y^{-1}$) | 640 ± 24 | 55 ± 14 | <0.001 |
| High-intensity training sessions* | 107 ± 6 | 12 ± 6 | <0.001 |
| Hemoglobin ($g \cdot dL^{-1}$) | 15.6 ± 0.3 | 15.3 ± 0.4 | NS |
| Creatinine ($\mu mol \cdot L^{-1}$) | 83 ± 3.5 | 85 ± 4.9 | NS |
| Total cholesterol ($mmol \cdot L^{-1}$) | 4.45 ± 0.22 | 5.01 ± 0.25 | <0.06 |
| HDL cholesterol ($mmol \cdot L^{-1}$) | 1.57 ± 0. 08 | 1.24 ± 0.11 | <0.02 |
| LDL cholesterol ($mmol \cdot L^{-1}$) | 2.41 ± 0.22 | 3.01 ± 0.24 | <0.07 |
| Triglycerides ($mmol \cdot L^{-1}$) | 1.0 ± 0.2 | 1.7 ± 0.3 | <0.03 |
| Glucose ($mmol \cdot L^{-1}$) | 4.9 ± 0.2 | 5.1 ± 0.1 | NS |
| Hb $A_{1c}$ (%) | 5.2 ± 0.1 | 5.3 ± 0.1 | NS |
| Insulin C-peptide ($nmol \cdot L^{-1}$) | 0.6 ± 0.1 | 0.9 ± 0.1 | <0.02 |
| Ferritin ($\mu g \cdot L^{-1}$) | 105 ± 18 | 151 ± 53 | NS |

Mean values ± *SEM*.

BMI = body mass index; BSA = body surface area; $\dot{V}o_2$max = maximal oxygen uptake; HDL = high-density lipoprotein; LDL = low-density lipoprotein; Hb $A_{1c}$ = glycolyzed hemoglobin A; NS = not statistically significant.

*High-intensity training sessions per year was defined as every session of exercise with >15 minutes of training at an intensity of 85% of maximal heart rate.

incline (0–5%) adjusted to the subject's fitness level, the incline was increased by 10%. The speed was thereafter increased by 1 $km \cdot h^{-1}$ every minute until exhaustion. To ensure that the maximal value was reached, two criteria had to be met: 1) A leveling-off of $\dot{V}o_2$ despite an increase of exercise power and 2) respiratory exchange ratio >1.05 (1).

#### Total Antioxidant Status Measurement

Total antioxidant status was measured in serum samples using the colorimetric Total Antioxidant Status assay (Randox). The method is based on 2,2'Azino-di-3-ethybenzthiazoline-sulfate (ABTS®) incubation with metmyoglobin and $H_2O_2$ to produce the radical cation ABTS®$^+$. This radical has a stable blue-green color that is measured at the wavelength of 600 nm. Antioxidants present in the added sample weaken the color intensity in proportion to their concentration. The assay was performed using an automated system and according to the manufacturer's instructions.

#### Total Nitric Oxide Assay

Quantitative determination of total nitrite ($NO_2^-$) concentration was performed using a commercially available total NO assay (R&D Systems, Inc., Minneapolis, MN). The assay determined total NO based on the enzymatic conversion of nitrate to nitrite by nitrate reductase. The reaction is followed by a colorimetric detection at 540 nm nitrite as an azo dye product of the Griess reaction. Briefly, frozen EDTA plasma was diluted twofold into reaction buffer and ultrafiltrated through a cutoff filter (Nanosep®; Pall Life Sciences) to eliminate proteins. All samples were analyzed in duplicate, and the assay was performed according to the manufacturer's protocol.

#### Statistical Analyses

All values are expressed as means ± *SEM*. A non-parametric test (Wilcoxon's signed ranks test) was used to make comparisons within groups. Between-group differences were calculated using the Mann-Whitney *U*-test. To test whether FMD might be related to arterial diameter and $\dot{V}o_2$max, Spearman's correlation coefficient was used. Statistical significance was defined as a two-tailed $P \leq 0.05$. A pilot study revealed that, for a given effect size (baseline arterial mean 4.0 vs. 3.5 mm), standard deviation 0.3 mm, sample sizes of 7 in each group, and $\alpha$ 0.05 (two-tailed), power was 0.816. We therefore chose to include 7–10 people in each group.

## Results

The trained group had 59% higher $\dot{V}o_2$max, 27% lower resting heart rate, and 21% lower body mass index than the sedentary group (Table 1). Low-density lipoprotein cholesterol and

triglycerides were 20% and 41% lower, whereas high-density lipoprotein was 27% higher among the athletes (Table 1).

Resting and maximal arterial diameters measured 1 minute after cuff release were 10–15% larger in the trained group before exercise and 1 hour, 24 hours, and 48 hours after the exercise session (Figure 2A, B). Peak blood flow after cuff release was 28–35% greater in athletes compared with untrained subjects (Figure 2C, D). Despite lower peak blood flow, untrained subjects had approximately 18% higher peak shear rate after cuff release at all time points compared with athletes (750.9 ± 11 vs. 640.2 ± 14 $s^{-1}$; $P < 0.01$). There were, however, no differences in FMD whether expressed in absolute terms (Figure 2A, B) or in percentages (Figure 2E, F) between groups at any time point, even when normalized to shear stress (data not shown). A 38% reduction in FMD was seen within the trained group 1 hour after exercise (Figure 2E, F). This postexercise reduction in FMD was accompanied by 6% and 7% enlargements of the resting arterial diameter among the trained sedentary groups, respectively (Figure 2A). GTN-mediated dilatation was 17% in both groups before exercise and did not differ within or between groups throughout the study.

We observed a significant inverse correlation between the resting diameter before exercise and FMD ($r = -0.48$,

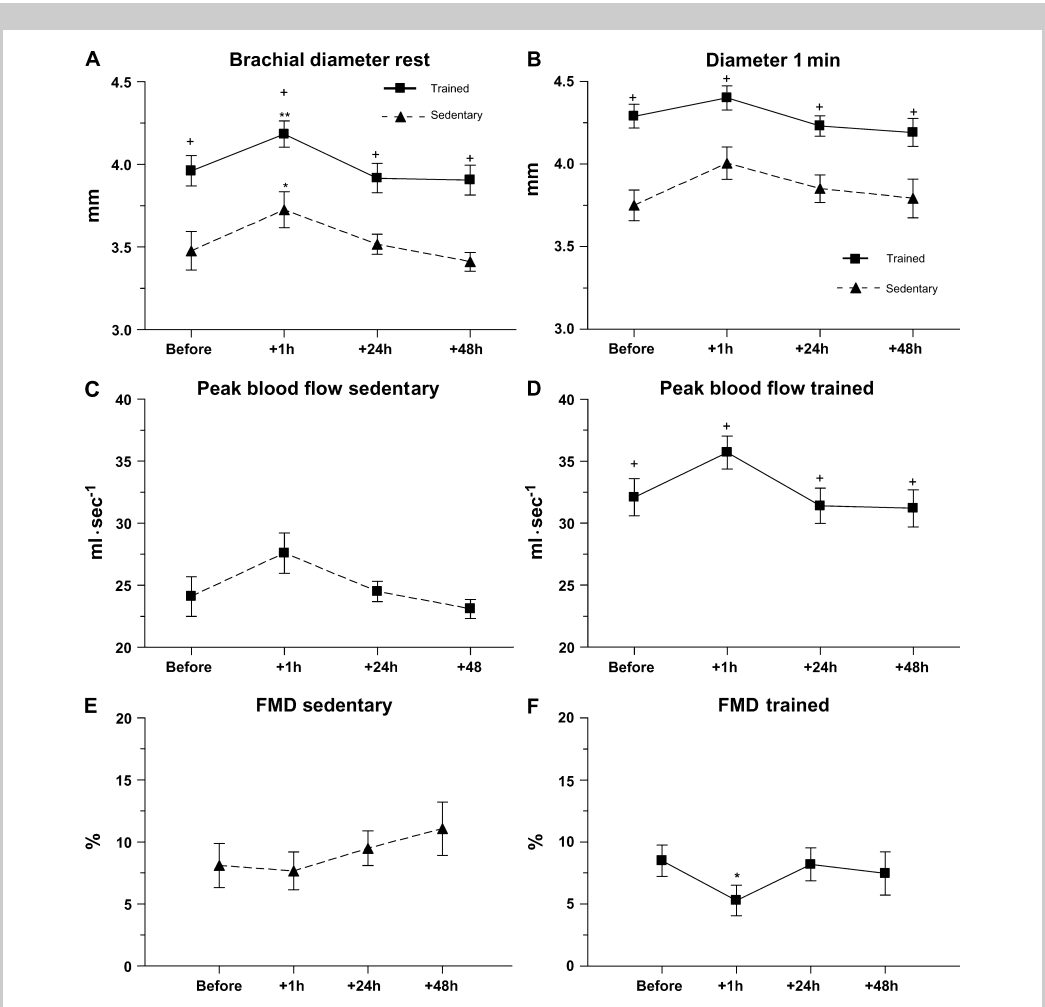


**Figure 2.** Brachial artery diameter (A, B), peak blood flow (C, D), and flow-mediated dilatation (FMD) (E, F) in endurance-trained and untrained men. *$P < 0.02$; **$P < 0.01$ vs. baseline. +Larger in the trained group at all time points ($P < 0.02$).

$P < 0.05$). Furthermore, our results showed a significant correlation between the resting diameters at baseline and $\dot{V}o_2max$ ($r = 0.59$, $P < 0.02$).

NO bioactivity did not differ between groups before the exercise session (Figure 3A). The NO level was, however, increased by 93% in the trained group and by 63% in the sedentary group 1 hour after training (Figure 3A). Interestingly, the NO bioactivity decreased to baseline level after 24 hours in the sedentary group but stayed elevated by 80% above baseline after 24 hours and by 93% after 48 hours in

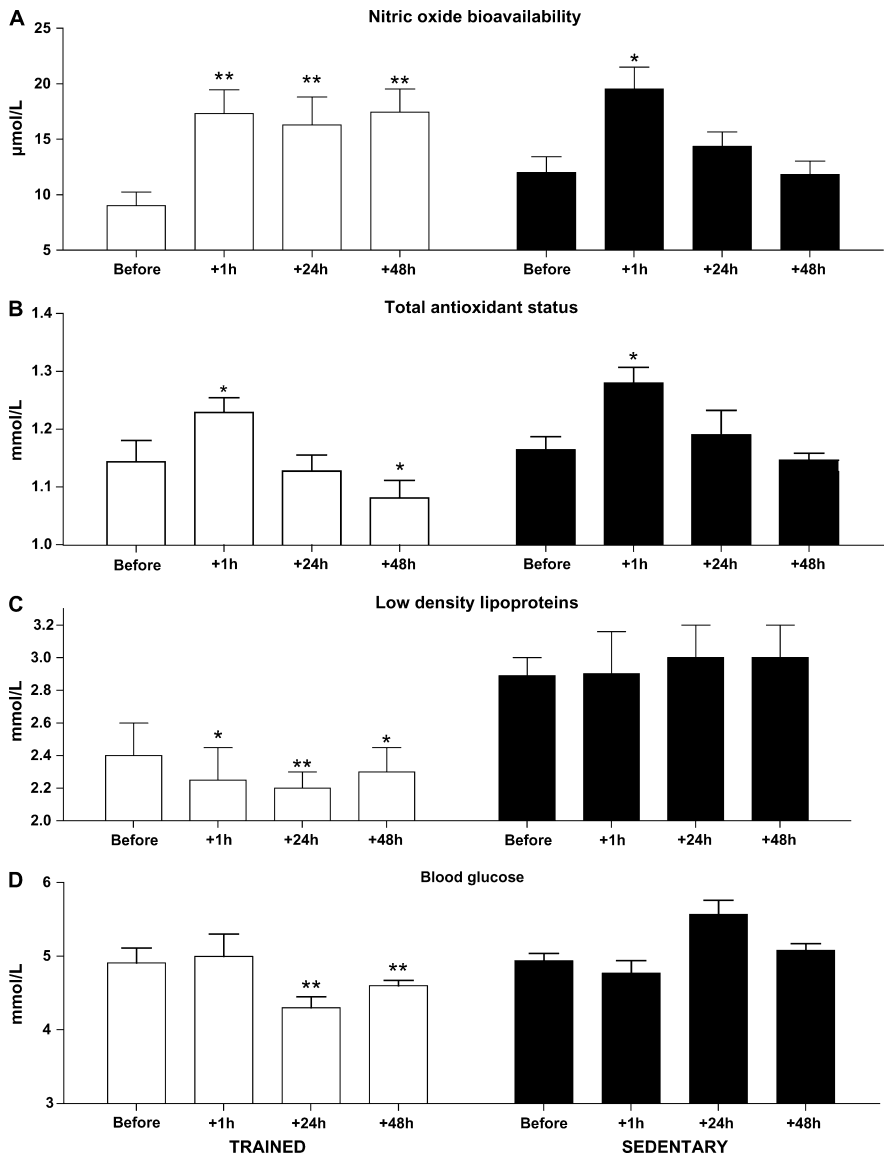


**Figure 3.** Nitric oxide bioactivity (A), total antioxidant status (B), low-density lipoproteins, and blood glucose levels measured before and after exercise. *$P < 0.05$; **$P < 0.02$ vs. before exercise within groups.

the trained group. Central to the regulation of endothelial function is the bioavailability of NO, and abnormalities in one or more pathways that ultimately regulate the availability of NO, such as the level of blood glucose, triglycerides, and high- and low-density lipoproteins, will influence endothelial function. The level of triglycerides was lower and high-density lipoproteins higher at all time points in the trained group (baseline values shown in Table 1), whereas a single bout of exercise significantly reduced the level of low-density lipoproteins and blood glucose (Figure 3C, D). The circulating antioxidant level was equal in the two groups before exercise (Figure 3B) and increased by 7% and 10% 1 hour post exercise in the sedentary and trained groups, respectively. The antioxidant status returned to baseline 24 hours after exercise in both groups and decreased to 5% below baseline ($P < 0.05$) (Figure 2B) in the trained group after 48 hours.

## Discussion

The main finding in the present study is that highly endurance-trained athletes had larger arterial diameter but similar endothelial-dependent vasodilatation when compared with untrained controls. Furthermore, we observed that the FMD response to acute endurance exercise was highly dependent on the time elapsed after exercise.

There were no significant differences in FMD between the groups at baseline. This indicates that the FMD, which is believed to be mediated mainly by NO, is well preserved in sedentary, young, healthy individuals and is not a limiting step for delivering large amounts of blood to the exercising musculature, as is the case during strenuous exercise. This is somewhat surprising considering that an average maximal oxygen uptake of 75.9 $mL \cdot kg^{-1} \cdot min^{-1}$ observed in the athletes in the present study requires a substantial higher cardiac output that has to be transported by the blood vessels to the exercising muscles compared with a $\dot{V}o_2max$ of 47.7 $mL \cdot kg^{-1} \cdot min^{-1}$ in untrained individuals (1).

In the present study, FMD measured 1 hour after the training session was significantly reduced compared with FMD at baseline in the trained group, whereas baseline values were observed 24 and 48 hours post exercise. This indicates impaired endothelial function 1 hour after the training session and normalization within 24 hours. Reduced FMD 1 hour post training indicates that oxidative radicals cause local vascular stress in the vessel during and after strenuous exercise. One could expect that super oxide-anion will quench NO (22) but that it will also combine with NO to form peroxynitrite (2), a reactive nitrogen species that uncouples eNOS by oxidizing the zinc-thiolate center, resulting in endothelial dysfunction because of reduced bioavailability and production of NO, respectively. However, in contrast to this, we observed increased bioavailability of NO (Figure 2A) and improved antioxidant status (Figure 2B) in blood samples taken 1 hour post exercise, suggesting that mechanisms other than NO and antioxidant levels are responsible for the transient decay in FMD observed in the endurance athletes.

Interestingly, Silber et al. (23) demonstrated that arterial FMD is linearly proportional to peak hyperemic shear stress in normal subjects, i.e., the endothelial response is linearly proportional to the stimulus. In line with this, we observed a significant inverse correlation between FMD and resting arterial diameter ($r = -0.51$, $P < 0.04$) and support earlier finding that larger arteries dilate less than smaller arteries (4,6). The greater FMD response in small arteries may be mediated, at least partially, by a greater hyperemic shear stress. In line with this, Silber et al. (24) recently demonstrated that the hyperemic shear stimulus for FMD was greater in small arteries because of the dependence of postischemic systolic flow on radius squared. Therefore, greater FMD in smaller arteries does not reflect better conduit artery endothelial function (24). Thus, it might be that FMD in the untrained controls, who had smaller artery diameters compared with the athletes, was overestimated. However, even when we normalized for shear rate, we could not observe any differences in FMD between the groups. The reason for this may be either that the present test of endothelial function is not sensitive enough to detect differences between a normal and supranormal endothelial function, or that a supranormal endothelial function not is necessary to deliver large amounts of blood to exercising muscles. However, because of the significantly larger diameter of the brachial artery and a normal FMD, the athletes have a substantially higher capacity to transport large amounts of blood during strenuous exercise compared with the untrained individuals, and as such they have improved "functional" endothelial function. Another interesting aspect was the large artery diameter observed in athletes 1 hour post exercise combined with high levels of NO in plasma, which probably dilated the vessel close to maximum, reducing the shear stress imposed by reactive hyperemia, thus reducing FMD. Recently, Hambrecht et al. (13) demonstrated twofold higher eNOS and a fourfold higher eNOS $Ser^{1177}$-phosphorylation level in the left internal mammary artery after 4 weeks of exercise training in patients with stable coronary artery disease compared with sedentary controls. The $Ser^{1177}$ residue seems to be a target for shear stress sensors, and phosphorylation of $Ser^{1177}$ leads to an increase in the enzyme activity of eNOS and enhanced NO production (11). Thus, exercise seems to have a dual positive effect by both increased protein expression of eNOS, which may take a few hours (9,11), and it enhances the phosphorylation of eNOS at $Ser^{1177}$ minutes after increased shear stress, thereby leading to increased vascular NO production. Interestingly, the shear stress-induced phosphorylation of eNOS is maintained (8), whereas agonist-mediated $Ser^{1177}$ phosphorylation, such as bradykinin, is only transient (10). Hambrecht et al. (13) showed that exercise training has a larger impact on phosphorylation of eNOS at $Ser^{1177}$ than on the expression of the eNOS protein itself. Sustained phosphorylation of eNOS could explain sustained increased NO production in athletes up to at least 48 hours post exercise. Furthermore,

a sustained increased level of NO for at least 48 hours occurred in conjunction with reduced levels of blood glucose and low-density lipoproteins, both known to be inversely related to the NO production. Interestingly, despite decreased levels of antioxidant capacity (i.e., increased level of reactive oxygen species) 48 hours post exercise in athletes, the bioavailability of NO remained 93% above baseline values, suggesting that the transient decrease in antioxidant status in athletes was physiologically insignificant.

Bergholm et al. (2) suggested that hard exercise may induce oxidative stress that impairs the endothelial function. They found that aerobic training (70–80% of $\dot{V}o_2max$) decreased the circulating antioxidant level and impaired the endothelial function in forearm vessels of healthy men after 4 weeks of running training. Interestingly, Bergholm et al. (2) performed the vascular measurements at least 36 hours after the last training session. Accordingly, their data for oxidative stress fit with ours, but, in contrast to their study, we found unchanged FMD and increased NO in blood at the same time point. The reason for this remains unknown but could be related to the much higher level of aerobic capacity in the athletes in the present study.

Athletes had larger arteries compared with the sedentary controls, and a large resting brachial artery diameter has been shown to be an independent predictor of significant coronary arterial disease (15). However, a larger arterial diameter with preserved function in athletes may be an analog to physiological hypertrophy of the athlete's heart with improved function vs. pathological hypertrophy (i.e., observed in patients with heart failure) with impaired function. Increased arterial diameter on the basis of an exaggerated stimulated production of NO in athletes suggests that a structural enlargement of the artery has taken place in athletes. The mechanisms responsible for mediating vascular structural enlargement are not fully understood, but there is strong evidence that NO plays an important part and that shear stress is the trigging factor (28). However, it seems that a larger brachial arterial diameter may be a stronger indicator of improved endothelial function than FMD when comparing highly trained and sedentary young subjects.

Low-density lipoprotein cholesterol and triglycerides were significantly higher in the sedentary group, whereas high-density lipoprotein cholesterol was significant higher in the trained group. The mean values were all in the normal range. In a recent study by our group, Moe et al. (19) reported no difference in FMD between highly trained and sedentary young women. The endurance-trained women had a higher high-density lipoprotein cholesterol value but similar low-density lipoprotein cholesterol and triglyceride values compared with the sedentary group. Similarly, Taddei et al. (27) reported the same endothelial function despite higher low-density lipoprotein and lower high-density lipoprotein cholesterol in a sedentary group compared with athletes (approximate mean age 27 years). This suggests that blood lipid values within the normal range do not affect the endothelial function, although it may influence NO production, as discussed above, in young, healthy subjects on a short-term basis. These findings contrast those of Steinberg et al. (26), who found that elevated cholesterol levels, even in the high normal range, may be associated with endothelial dysfunction. The mean age in Steinberg et al.'s study was approximately 32 years, compared with approximately 24 years in our study. Thus, endothelial dysfunction may be a long-term effect that is not apparent in early adulthood among nonobese individuals. Kingwell et al. (17) showed improved endothelial function in endurance athletes aged approximately 35 years compared with age-matched sedentary men. A covariance analysis suggested that a lower total cholesterol level in the trained group contributed to the enhanced vasodilator response. This supports the hypothesis that total cholesterol level influences the endothelial function more with increasing age. Finally, De Souza et al. (7) reported similar endothelial function and blood lipid profiles in healthy sedentary men compared with trained young men.

The results of the present study suggest that endothelial function is well preserved in young, healthy men and that a high aerobic training status because of long-term aerobic training does not improve the dilating capacity. However, the transporting capacity of blood is greater in athletes because of their larger artery diameter. In addition, one strenuous high-intensity exercise session does not seem to impair endothelial function.

## Practical Applications

The current study demonstrates that the differences in artery diameter, not the ability of the vessel to dilate per se, distinguish the enormous transport capacity of blood in athletes' arteries from that in normal healthy individuals. Large arteries in athletes are linked to good function, whereas large arteries in untrained subjects are linked to poor function. Thus, "the athlete's artery" is an analog to the athlete's heart with good function vs. the pathological hypertrophied heart with poor function.

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# PAPER IV

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## Dissertations at the Faculty of Medicine, NTNU

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