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Aerobic exercise in coronary heart disease

Thesis for the degree of Philosophiae Doctor

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Utholdenhetstrening hos personer med koronar hjertesykdom

Fysisk inaktivitet er en risikofaktor for koronar hjertesykdom (CHD). Friske personer som er fysisk aktive har både lavere dødelighet totalt og lavere dødelighet av CHD sammenlignet med personer som ikke er fysisk aktive. Det finnes mindre data på assosiasjonen mellom fysisk aktivitet og dødelighet blant personer med allerede etablert CHD, men det ser ut til at fysisk aktivitet er forbundet med redusert dødelighet også her. Det er fortsatt en del ubesvarte spørsmål om denne assosiasjonen blant personer med CHD, spesielt i forhold til hvor mye og hvor intens fysisk aktivitet som skal til for å redusere dødeligheten. Med data fra en stor befolkningsundersøkelse, Helseundersøkelsen i Nord-Trøndelag (HUNT-1), undersøkte vi assosiasjonen mellom fysisk aktivitet og dødelighet blant 2137 menn og 1367 kvinner med CHD. Sammenlignet med referansekategorien (ingen aktivitet), var trening en gang i uka assosiert med redusert dødelighet hos begge kjønn. Personer som trente mer enn en gang i uka hadde ytterligere reduksjon i dødelighet, og trening med moderat eller høy intensitet ga større reduksjon enn trening med lav intensitet.

Siden kondisjon målt som oksygenopptak er en sterk prediktor for død hos hjertepasienter, bør man finne effektive måter å øke kondisjonen blant CHD-pasienter. Vi undersøkte betydningen av treningsintensitet i to kliniske forsøk. Femtini koronar bypass-opererte (CABG) pasienter ble tilfeldig fordelt til enten intervalltrening (AIT) på 90 % av maksimal hjertefrekvens, eller moderat kontinuerlig trening på 70 % av maksimal hjertefrekvens, fem dager i uka i fire uker ved et rehabiliteringssenter. Oksygenopptaket økte signifikant i begge grupper etter treningsperioden, men det var ingen forskjell mellom gruppene. Etter seks måneders hjemmetrening hadde bare AIT en fortsatt økning i oksygenopptak.

Åttini pasienter med hjerteinfarkt (MI) ble tilfeldig fordelt til AIT på tredemølle ved 90 % av maksimal hjertefrekvens eller til gruppetrening gitt som standard behandling ved tre norske sykehus. Maksimalt oksygenopptak økte signifikant mer etter AIT på tredemølle enn etter gruppetrening. De som trente på tredemølle hadde høyere treningsintensitet enn de i gruppetrening. Blodårefunksjon økte signifikant i begge gruppene. Livskvalitet økte signifikant etter trening hos både CABG- og MI-pasientene.

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Contents

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Most of all, I want to thank Viggo for being my kind and always optimistic husband. You are the best! Martine and Christian, both born during these years; I want to thank you for giving me joy and laughter every day.

Errata

Paper II

Figure 1, left column should be ”leg pain” (not ”legg”)

Table III, legends: e’ and a’ should be named early/late diastolic annular velocity

List of papers

The studies presented in this thesis were carried out at the Norwegian University of Science and Technology, Faculty of Medicine, Department of Circulation and Medical Imaging, during the years 2004-2009. The working hypothesis of the project was that physical activity in general, and high intensity exercise in particular, will increase aerobic capacity and associate with reduced mortality in subjects with coronary heart disease. The included original articles are listed below and referred to by their roman numbers.

Paper I

Moholdt T, Wisløff U, Nilsen TI, and Slørdahl SA. Physical activity and mortality in men and women with coronary heart disease: a prospective population-based cohort study in Norway (the HUNT study). *Eur J Cardiovasc Prev Rehabil 2008;15:639-45*

Paper II

Moholdt, T, Amundsen, BH, Rustad, LA, Wahba, A, Løvø, KT, Gullikstad, L, Bye, A, Skogvoll, E, Wisløff, U, Slørdahl, SA. Aerobic interval training versus continuous moderate exercise after coronary artery bypass surgery: A randomised study of cardiovascular effects and quality of life. *Am Heart J 2009;158:1031-7*

Paper III

Moholdt, T, Aamot, IL, Granøien, I, Gjerde, L, Myklebust, G, Walderhaug, L, Brattbakk, L, Hole, T, Graven, T, Stølen, T, Amundsen, BH, Hansen, HEM, Støylen, A, Wisløff, U, Slørdahl, SA. Does treadmill aerobic interval training increase peak oxygen uptake more than group exercise training in myocardial infarction patients? A randomized, controlled study. *Submitted*

Abbreviations

A: late diastolic mitral flow velocity

a': late diastolic mitral velocity

AIT: aerobic interval training

CABG: coronary artery bypass grafting

CHD: coronary heart disease

DT: deceleration time of early diastolic mitral flow velocity (E)

E: early diastolic mitral flow velocity

e': early diastolic mitral velocity

E/A: the ratio of early diastolic to late diastolic mitral flow velocity

EF: ejection fraction

FMD: flow mediated dilatation

HR: heart rate

HUNT: Nord-Trøndelag health study

MCT: moderate continuous training

MET: metabolic equivalent

MI: myocardial infarction

NO: nitric oxide

PCI: percutaneus coronary intervention

VO_{2peak}: peak oxygen uptake

Definitions

Angina pectoris (AP): Chest pain due to ischemia of the heart muscle, generally due to obstruction or spasm of the coronary arteries.

Confidence interval (CI): A quantity of the uncertainty in estimation. It is often reported as 95% CI, which is the range of values within which we can be 95% sure that the true value for the whole population lies.

Coronary heart disease (CHD): Failure of coronary circulation to supply adequate blood to the cardiac muscle. It is most commonly caused by atherosclerosis.

Endurance training: Activity in which the body's large muscles move in a rhythmic manner for a sustained period of time. Examples include walking, running, and swimming.

Lactate threshold: The exercise intensity at witch a sudden and sustained increase in blood lactate concentration is seen. This rise is due to a higher production than elimination of lactate in the muscles at intensities above the lactate threshold.

Maximal oxygen uptake (VO_{2max}): The body's capacity to transport and use oxygen during a maximal exertion whole-body exercise, while breathing air at sea level.

Myocardial infarction (MI): Myocardial cell death due to prolonged ischemia, which is the result of a perfusion imbalance between supply and demand.

Peak oxygen uptake (VO_{2peak}): The highest oxygen uptake achieved when all the criteria for VO_{2max} can not be fulfilled.

Physical activity: Any bodily movement produced by skeletal muscles that substantially increases energy expenditure.

Relative risk: The risk of a (typically) adverse health outcome among an exposed group compared to an unexposed group. In physical activity, relative risk is typically the ratio of the risk of mortality when comparing groups of people with varying amounts of physical activity.

Work economy: The mechanical efficiency, that is, the ratio of work done to energy expended.

Summary

Physical inactivity is recognised as a risk factor for coronary heart disease (CHD). Healthy subjects who exercise have lower all-cause and CHD mortality compared to inactive. Also in subjects with already established CHD, being physically active seems to be associated with reduced mortality, but less data exist. Especially, the amount and intensity of exercise required for risk reduction in CHD patients is not yet fully resolved. With data from a population based prospective cohort study, the Nord-Trøndelag health study (HUNT-1), we investigated the association between physical activity and mortality in 2137 men and 1367 women with CHD. Compared to the reference category (no activity), one weekly exercise session was associated with reduced mortality in both genders. This inverse association became stronger with increasing exercise frequency and subjects reporting of moderate/high intensity exercise had a lower mortality risk than subjects reporting of low intensity exercise.

As peak oxygen uptake (VO_{2peak}) strongly predicts mortality in cardiac patients, it is warranted to find effective ways to increase aerobic fitness in CHD patients. We investigated the impact of exercise intensity for improvements in VO_{2peak} in two clinical trials. Fifty-nine coronary artery bypass surgery (CABG) patients were randomised to either aerobic interval training (AIT) at 90% of maximum heart rate, or moderate continuous training (MCT) at 70% of maximum heart rate, five days/week, for four weeks at a rehabilitation centre. VO_{2peak} increased significantly in both groups after the training period, with no difference between groups. After six months of home exercise, only the AIT group had a further increase in VO_{2peak}.

Eighty-nine myocardial infarction (MI) patients were randomised to treadmill AIT at 90% of maximum heart rate or to the group exercise programs provided by three Norwegian hospitals as usual care. VO_{2peak} increased significantly more after treadmill AIT than after group exercise. Endothelial function, measured as flow-mediated dilatation, increased significantly in both groups. Health related quality of life increased significantly after exercise training in both CABG and MI patients.

Being physically active was associated with reduced mortality in subjects with CHD. For CABG patients at a rehabilitation centre for four weeks, both AIT and MCT gave significant increase in VO_{2peak}, while six months later only the AIT group had a further increase. We found larger increase in VO_{2peak} after treadmill AIT than after the group exercise training provided as usual care to MI patients by three Norwegian hospitals.

Introduction

Cardiovascular disease is the leading cause of death in Europe accounting for 48% of all deaths. Just under half of the cardiovascular deaths are from coronary heart disease (CHD), which is the single most common cause of death in Europe [1]. It is estimated that 5-10% of all deaths and over 20% of CHD deaths in developed countries are caused by physical inactivity [2].

Physical activity, fitness and mortality

Numerous epidemiological studies have reported decreased risk for both all-cause mortality and cardiovascular mortality in subjects who are physically active [3-6] or have high exercise capacity [7-11]. Moreover, physical activity decreases the risk of many diseases, among others cardiovascular disease [12, 13], type 2 diabetes mellitus [14, 15], some cancers [16, 17], and depression [18]. Although the prevalence of physical inactivity declined in USA between 1994 and 2004, still almost every fourth American reported of no physical activity in leisure-time [19]. In 2008, the prevalence of physical inactivity for a pooled sample of 51 countries (for the most developing countries), were about 15% for men and 20% for women [20]. In the just finished data collection for the third Nord-Trøndelag health study (HUNT-3), 22% reported of no physical activity or less than once weekly activity, and 57% reported of exercising two times or more per week (personal communication). The most recent recommendations state that healthy adults should be moderately physically active 30 minutes or more five days per week, or vigorously active 20 minutes three times per week [21]. A recent study showed that these activity levels were associated with significantly longer survival compared to no physical activity [6]. The range of reductions in relative risks in physically active subjects varies somewhat between studies. In a recent review, Nocon et al [22] estimated that in general, physical activity reduced all-cause mortality by 33% (95% confidence interval, 28-37%) and cardiovascular mortality by 35% (95% confidence interval, 30-40%) in healthy subjects.

Some epidemiological studies also exist on the association between physical activity and mortality in CHD patients [23-29]. Although one of these studies found higher mortality rates in asymptomatic CHD subjects who were physically active [29], the studies altogether indicate that physical activity reduces mortality also in subjects with

CHD. In these patients too, a curvilinear relationship between physical activity level and mortality risk has been suggested, with the greatest reductions in mortality risk in the lower end of the scale, with a levelling off at higher levels [27]. However, many of the existing studies are somewhat limited by small numbers of participants [23, 25, 26, 29, 30], investigating only one gender [23, 24, 26, 29-31], or having age limits [23-25, 27]. Due to the restricted numbers of participants, some of the studies had to dichotomize the subjects into active versus sedentary [23, 25]. In all of the remaining studies, exercise intensity was categorized according to absolute intensities [24, 26-29]. Subjects with CHD have a reduced exercise capacity and are often elderly, and therefore the relative intensity of certain activities may be higher than in younger and fitter subjects. Despite of the well documented association between physical activity and longevity, the exact shape of the dose-response curve remains unclear, both for healthy subject and also for CHD patients. Regarding healthy subjects, there are indications in the literature that the greatest reduction in mortality is seen when going from inactivity to the minimal activity category [4, 32, 33]. For instance, Wisløff et al [4] found a positive association between physical activity and survival, but the greatest increase in life length was seen between the ones being physically active once per week compared to no activity. Reduced physical *capacity* is shown to be a strong predictor of mortality in healthy subjects and subjects with CHD, as an increase in maximal oxygen uptake of 1-3.5 $mL \cdot kg^{-1} \cdot min^{-1}$ has been reported to be associated with ~15% improvements in survival [7, 34].

In summary, based on the current knowledge, physical activity is recommended as a means to increase life expectancy both for healthy and CHD subjects. However, the optimal amount and intensity of physical activity needed for protection against cardiovascular and all-cause mortality remains unclear, especially in subjects with CHD. In particular, there is a need to investigate whether there is an additional benefit of high intensity exercise in CHD subjects with regard to mortality.

Maximal oxygen uptake (VO_{2max})

A person's maximal oxygen uptake (VO_{2max}) can be defined as the highest rate at which oxygen can be taken up and used by the body during dynamic exercise using large muscle groups [35], and has been regarded as the gold standard for aerobic fitness [36].

VO_{2max} is the product of cardiac output and arteriovenous oxygen (a-vO_2) difference, as shown by the Fick equation:

VO_{2max} = (HR x SV) x a-vO_2 difference,

where HR indicates heart rate and SV indicates stroke volume [37]. Any physiological structure or process that determines these variables would therefore potentially limit VO_{2max}. Although there still exists some disagreement about what limits VO_{2max} [38], most researchers agree that in healthy, non-athletic subjects performing maximal whole body exercise at sea level, the cardiac output is the predominant limiting factor [35, 39, 40]. Less fit subjects, like most CHD patients, are thought to be more restricted by peripheral factors [41]. Due to the often observed inability to reach a plateau of VO_2 during exercise testing in patients with cardiovascular disease, peak oxygen uptake (VO_{2peak}) is sometimes used instead of VO_{2max} [37]. VO_{2peak} is then the highest oxygen uptake reached in a maximal effort exercise test.

How much VO_{2max} increases after a period of exercise training, is dependent upon the intensity, frequency, and duration of each exercise session, as well as the length of the training programme, and the initial fitness level of the subject. Exercise intensity has been argued to be the key factor in producing improvements in VO_{2max} since increasing intensity up to 100% of VO_{2max} produces the greatest improvements across all frequencies, durations, programme lengths and initial fitness levels of the subjects [42].

Exercise intensity

Exercise intensity can be described in terms of both relative and absolute intensity. Absolute intensity is the amount of external work that is being done by the subject, denoted for example in Watts, metabolic equivalent (METS) or walking speed. Relative intensity, in contrary, is the intensity of an activity expressed in relation to the capacity of the subject or as a subjective level of effort. Studies comparing equal volumes, and thus energy expenditure, of moderate and high intensity exercise training, have found significantly larger increases in VO_{2max} after high (relative) intensity interval training in healthy subjects [43, 44] and in subjects with coronary heart disease [45], heart failure [46], the metabolic syndrome [47], and intermittent claudication [48]. Also, a recent review of

both epidemiological studies and clinical trials concluded that high intensity exercise appears to give greater cardioprotective benefits than moderate intensity exercise for healthy individuals [49].

High intensity interval training can be defined as repeated bouts of short to moderate duration exercise (i.e. 10 seconds to 5 minutes) at intensities above the lactate threshold. The exercise bouts are separated by brief periods of lower intensity work allowing partial but often not full recovery [50]. In contrast, moderate intensity exercise is typically performed as continuous work and is below the lactate threshold [51].

Exercise training in cardiac rehabilitation

Cardiac rehabilitation has been defined by the World Health Organisation [52] as "the sum of activities required to influence favourably the underlying cause of the disease, as well as to ensure the patients the best possible physical, mental and social conditions so that they may, by their own efforts, preserve, or resume when lost, as normal a place as possible in the life of the community" (p 5). As physical inactivity is recognized as an important risk factor for progression of established CHD, exercise training is regarded as one of the core components in cardiac rehabilitation [53, 54]. Although no single randomised controlled trial has yet shown decreased mortality after cardiac rehabilitation, several meta-analyses show a 20-31% reduction in mortality for CHD patients who participate in exercise based cardiac rehabilitation [55-58].

American and European recommendations on aerobic exercise training in patients with CHD state that the exercise intensity should be 50-85% of VO_{2max}, corresponding to about 60-93% of maximum heart rate (HR). Further, it is recommended to exercise 3-5 days per week for 20-60 minutes each time, either as continuous or interval training with large muscle groups [53, 59, 60].

Adaptations to exercise training in CHD patients

Exercise training give rise to several physiological adaptations in CHD patients. In the following paragraphs some of these adaptations are presented, with focus on adaptations after aerobic exercise training (endurance training). The majority of the published studies on exercise training of CHD patients have used low or moderate exercise intensities [61-70], but a few studies report of exercising up to 90-95% of individual

maximum HR [45, 46, 71-73]. Since superior cardiovascular effects have been seen after aerobic interval training (AIT) compared to moderate continuous training (MCT) in healthy subjects and several patient groups [43-48], further studies on the effects of AIT in CHD patients are justified. Especially, there is a need to see if, and how, AIT can be used in clinical settings.

Aerobic capacity

A person's aerobic capacity is determined by the VO_{2max}, the lactate threshold and work economy. Randomised controlled trials comparing exercise training with no training report 15-30% improvements of $VO_{2max/peak}$ in CHD patients after exercise training [61, 62, 67, 68, 71, 74]. Also indirect indices of aerobic capacity, like exercise time or external work performed, has been reported to increase after exercise training compared to no training in CHD patients [63, 65, 66, 69]. Further, changes have been seen in lactate threshold [71, 72] after exercise training in CHD patients. Better work economy has been found after strength training in CHD patients [75], but is less studied after aerobic endurance training in these patients.

Left ventricular function

Since maximal HR is minimally affected by exercise training, increased stroke volume is the only optional explanation of increased cardiac output. Stroke volume is determined by left ventricular pre- and afterload, and myocardial contractility. Left ventricular preload is set by active and passive tissue properties, by the pressure in the left atrium, and HR. An adequate diastolic function is necessary to ensure a sufficient preload during exercise. When directly measuring left ventricular pressures in resting MI patients with left ventricular dysfunction, Miyashita et al [76] found that only variables of left ventricular diastolic function – and not systolic function – were significantly correlated to VO_{2peak}. During exercise, both systolic and diastolic function variables were correlated to VO_{2peak}, but diastolic variables more closely than systolic [76]. Using echocardiography at rest and post exercise, reduced diastolic function grade and high left ventricular filling pressures have been found to be independently associated with low exercise capacity in a population free of valvular heart disease or ischemia [77]. Also

Skaluba et al [78] found left ventricular filling pressures to be the strongest echocardiographic predictor of exercise capacity.

Both diastolic and systolic left ventricular function have previously been found to improve in CHD patients after a period of exercise training [69, 79-81]. Yu et al [80] found no significant change in the proportion of patient with diastolic dysfunction after exercise training in MI or elective percutaneous coronary intervention (PCI) patients. However, in the control group they saw an increased proportion of the patients having an abnormal relaxation pattern after the intervention period. Further, when analysing only the MI subgroup, they found significantly increased early mitral flow velocity (E) as well as shortening of the deceleration time of the early diastolic mitral velocity (DT) after the exercise period. They saw that the changes in E correlated positively with gain in exercise capacity in the patients with an abnormal relaxation pattern [80]. In contrast, others have reported of no significant changes in diastolic parameters after 16 weeks of exercise training in patients with diastolic dysfunction [82]. Koizumi et al [69] found increased left ventricular ejection fraction (EF%) and end diastolic volume *during* exercise after three months of walking in MI patients without heart failure, compared to a control group. *At rest* they saw no changes in these indices after the training period, indicating an actual improvement in diastolic and systolic function only during exercise. Few previous studies have looked upon both diastolic and systolic function, and none has yet included aerobic interval training, in CABG patients.

Endothelial function

The endothelium is the inner cell layer of the arteries, and can be regarded as the largest endocrine organ of the human body [83]. Among others, one important function of the endothelium is to control the vasomotor tone in the vasculature. Additionally, it is the place for synthesis and release of various cytokines and growth factors, as well as the turnover and oxidation of the lipoproteins in the arterial wall [83]. Endothelial dysfunction is one of the most important visible changes in the early subclinical stage of atherosclerotic disease [84], and the grade of dysfunction is related to the extent and severity of CHD [85]. Further, impaired endothelial function has been found to be a strong independent risk factor for future cardiac events [86-90].

The vasomotor tone in the vascular bed is a result of the balance between relaxation and contraction in the smooth muscles. There are several factors that determine if the vessels should constrict or dilate, and the most important vasodilator of endothelial origin is considered to be nitric oxide (NO) [91, 92]. As a response to increased shear stress caused by increased blood flow, a healthy blood vessel dilates. This condition is called flow-mediated dilatation (FMD)[83] and NO is though to be responsible for FMD because of its known vasodilator effect [93]. FMD can be measured in the brachial artery by the use of high resolution ultrasound with 2D images of the artery in the longitudinal plane [94]. A sphygmomanometer is placed either above the antecubital fossa or on the forearm and inflated to a pressure well above the systolic pressure of the subject to stop the antegrade blood flow. After five minutes of occlusion, the sphygmanometer is deflated and reactive hyperemia will occur in the artery. The % difference between the basal diameter and the diameter after the deflation is FMD [94].

Exercise training has been shown to increase FMD in CHD patients [46, 71, 95], and such improvement in endothelial function may represent an important mechanism by which exercise provides cardiovascular benefit. The most important factor in restoring normal endothelial function after exercise training is probably the ability to increase the endothelial bioavailability of NO. This is presumably caused by a restoration of the balance between NO production and NO inactivation by reactive oxygen species [96], and by up-regulating the enzyme endothelial nitric oxide synthase (eNOS) [97]. In subjects with the metabolic syndrome and in heart failure patients, AIT has given larger improvements in FMD than moderate continuous exercise [46, 47]. In MI patients, similar significant increases in FMD were seen after four weeks of aerobic training, strength training and strength plus aerobic training [95]. In a recent study, Munk et al [71] found significantly increased FMD after AIT in MI patients treated with percutaneous coronary intervention (PCI) with stent implantation. In their study, the control group did no exercise training [71]. Further studies on the effect of AIT compared to other exercise protocols on FMD in MI patients are therefore warranted.

Heart rate recovery

HR recovery is the decline in HR after cessation of a maximal effort exercise test. The difference between the HR at maximum and at one minute after ending the test is most often used as the HR recovery [61, 98-100]. Studies have shown that HR recovery is a

predictor of mortality both in healthy subjects and in patients referred for exercise testing [100, 101]. Autonomic dysfunction is a possible mechanism linking slow HR recovery to increased mortality, as the autonomic nervous system has been extensively implicated in the triggering of sudden cardiac death [102]. HR recovery has previously been found to increase after a period of exercise training in patients with acute myocardial infarction [61], in CABG patients [74], and in heart failure patients [103]. The impact of exercise intensity on changes in HR recovery in CHD patients is however not established.

Circulating biomarkers of CHD

Biomarkers may serve as surrogate end points to evaluate the effectiveness of a treatment [104]. The most useful circulating biomarker for cardiovascular risk stratification, therapeutic monitoring, and prognosis is not yet settled, and maybe are the traditional markers, like blood lipids, glycemic status, and C-reactive protein (CRP), not the most important. Increasing attention has been paid to plasma proteins that originate from adipose tissue, and especially adiponectin has emerged as a relevant and important biomarker of cardiovascular risk [105]. Adiponectin is a cytokine with antiatherogenic effects as it stimulates the production of NO [106], inhibits monocyte adhesion to endothelial cells [107], suppress both endothelial cell apoptosis [108] and the conversion of macrophages to foam cells [109]. Further, hypooadipionectinemia is associated with endothelial dysfunction [110] and plasma levels of adiponectin are negatively correlated with adiposity [111], the risk of type 2 diabetes [112], and CHD [113]. Increased serum adiponectin levels has been reported after exercise training [47, 114], but data are conflicting [115]. Of interest, there exists little information on the effect of exercise training on adiponectin levels in CHD patients.

Quality of life

When speaking about quality of life throughout this thesis, the focus is *health related* quality of life. Currently there exists no agreement on a single definition of health related quality of life, but most instruments measuring it include at least some items that cover domains of physical, emotional and social functioning [116]. A recent review has revealed a consistently positive association between level of physical activity and

quality of life in the general population [117]. Quality of life outcome measures have also been considered increasingly important in the evaluation of randomised controlled trials [118]. The reason for measuring quality of life, is to get a picture of the patient's perception of the functional effect of an illness and its therapy [119]. Although cardiac rehabilitation programmes traditionally have concentrated upon physical functioning, several studies have reported increased quality of life after cardiac rehabilitation [63, 67, 120-123]. Despite this, it has been concluded that there are not sufficient documentation of an effect of cardiac rehabilitation on quality of life above usual care [56].

Safety of exercise training in cardiac patients

Although physical activity is widely advocated in primary and secondary prevention of CHD, exercise can also acutely and transiently increase the risk of acute MI and sudden cardiac death in susceptible subjects [124, 125]. In supervised cardiac exercise programs, the rate of cardiac arrest, MI and fatality was estimated to be 1 per 116 906, 1 per 219 970 and 1 per 752 365 patient-hours of exercise, respectively [126]. In spite of this, the benefits of exercise training surely outweigh the possible risks [126]. Moreover, even though vigorous exercise triggers sudden cardiac death, habitual vigorous exercise diminishes the risk [124]. In stable CHD patients participating in vigorous group exercise, it was found that adherence to an exercise intensity of < 95% of maximal HR seldom elicits ischemia [127].

Long-term adherence to exercise prescriptions

One of the greatest challenges in the field of cardiac rehabilitation today is how to motivate the patients to continue with a healthy lifestyle after ending a formal rehabilitation program [128]. In contrast to the well established short-term benefits of cardiac rehabilitation, documentation of the sustainability of these benefits is scarce. There are indications of both unchanged, decreased, and increased aerobic capacity at follow-up testing 12-24 months after ending the formal program [129-133].

Objective and hypotheses

The primary aims of the studies were to:

1. Investigate the association between self-reported amount and intensity of exercise training and mortality in patients with coronary heart disease (CHD) using a large, unselected population (the Nord-Trøndelag Health Study, HUNT-1).

Hypothesis: Physical activity is associated with reduced mortality in CHD subjects.

2. Compare the effects of aerobic interval training (AIT) versus moderate continuous training (MCT) upon peak oxygen uptake (VO_{2peak}) after coronary artery bypass grafting (CABG).

Hypotheses: Four weeks of AIT increases VO_{2peak} more than MCT in CABG patients. At follow-up six months later, there will be no difference between the groups.

3. Compare the effects of the group exercise training provided as usual care by three Norwegian hospitals versus treadmill AIT upon VO_{2peak} in myocardial infarction (MI) patients.

Hypothesis: Treadmill AIT increases in VO_{2peak} more than group exercise training in MI patients.

Materials and methodological considerations

Subjects

The subjects in this thesis were patients with coronary heart disease (CHD); both angina pectoris, myocardial infarction (MI), and bypass surgery (CABG) patients (Table 1). Inclusion and exclusion criteria are described in the papers.

Table 1. Overview of the subjects included in the thesis

	Patient group	Men	Women
Paper I	Angina pectoris and/or myocardial infarction	2137	1367
Paper II	Coronary artery bypass	48	11
Paper III	Myocardial infarction	74	15

Paper I

In 1984-1986 the first part of the Nord-Trøndelag Health Survey (HUNT-1) was conducted. All residents in Nord Trøndealg county aged 20 years or more were invited to participate. Nearly 90% of 85,100 eligible persons filled in the questionnaire mailed to them together with the invitation letter. In addition, a second questionnaire was handed out at a health examination, together with a pre-stamped envelope. This questionnaire contained queries on several medical and lifestyle factors, including physical activity. A more comprehensive description of the survey can be found in Holmen et al [134]. In paper I we have used the subgroup of CHD patients in the HUNT database, based on their self-reported MI or angina pectoris at baseline of the survey (in 1984-1986) (Table 1). The population of Nord-Trøndelag has been regarded as quite representative for the Norwegian population as a whole. Further, the population based design of HUNT is one of the strengths of this survey in comparison with other large

epidemiological surveys often using selected subgroups of a population (for example university alumni or certain occupational groups) [3, 14, 29, 135].

Paper II

The CABG patients in paper II were recruited by a posted invitation sent out by the rehabilitation centre where the study took place. Out of 110 eligible patients, 69 accepted to participate in the study, and 59 patients completed the study protocol (Table 1). The subjects who participated in the study were somewhat younger than the ones excluded (61.1, SD 7.4 versus 66.7, SD 7.9 years). There was also slightly less women relative to men who participated than who got excluded (11/69 and 10/41, respectively).

Paper III

In paper III we included 107 MI patients from three Norwegian hospitals. With 18 drop outs, we analysed data on 89 patients (Table 1). The mean age of the subjects in our study was 57.4 (SD 9.5) years, which is lower than the mean age of subjects with MI at the cardiac section at the largest hospital in the study (72.2 years for women and 64.7 years for men). Also, the portion of women relative to men in the study (13/89) was lower than the portion among all subjects with MI (30/100) in the region.

Measurements

In paper I, the primary outcome measure was all-cause mortality. Secondary measures were cardiovascular mortality and ischemic heart disease mortality. In both paper II and III changes in peak oxygen uptake (VO_{2peak}) were the primary outcome measure. However, besides an increased VO_{2peak}, there are several other physiological adaptations to exercise training. The adaptations investigated in this thesis comprise left ventricular function (paper II), endothelial function (paper III), resting heart rate (HR) (paper II and III), HR recovery (paper II and III), work economy (paper II) and some blood markers of cardiovascular disease (paper II and III). We also investigated changes in quality of life in paper II and III.

Questionnaire in paper I

The questionnaire in paper I had three questions regarding exercise, one on the frequency, one on the duration, and one on the intensity of exercise (Table 2).

Table 2. Questions on exercise frequency, duration and intensity in the Nord-Trøndelag Health Study (HUNT-1)

EXERCISE
By exercise we mean going for walks, skiing, swimming and working out/sports.
How often do you exercise? (on the average)
Never
Less than once a week
Once a week
2-3 times a week
Nearly every day
If you exercise as often as once or several times a week:
How hard do you exercise?
(average)
I take it easy, I don't get out of breath or break a sweat
I push myself until I'm out of breath and break into a sweat
I practically exhaust myself
For how long do you exercise each time? (average)
Less than 15 minutes
16 - 30 minutes
30 minutes - 1 hour

A relative scale was used to measure the intensity of the exercise, as the subjects' own feeling of intensity was recorded. The relative intensity of exercise has previously been shown to better distinguish risk than absolute intensity [136]. The questions regarding physical activity in HUNT-1 used the Norwegian word "mosjon". This can be translated into exercise or physical activity, and in this thesis as well as in paper I, these terms are used interchangeably. As explained in the headings in the questionnaire, the exercise included for example to go for a walk, cross country skiing, swimming or sports. The subjects were asked to take the average for a week representing the whole year, and this was a way to overcome the seasonal variations [137]. The HUNT-1 questionnaire did not discriminate between physical activity in leisure and during work, or on the way to and

from work. The exercise questions have been validated according to tests of VO_{2max}, and there was no difference by age or sex in reporting exercise intensity or in observed exercise intensity relative to VO_{2max} [4].

Exercise testing

VO_{2peak} was measured on treadmills in paper II and III. Walking or jogging on a treadmill provides a common form of physiologic stress in which the subjects are more likely to attain a slightly higher oxygen uptake and HR than during testing on a stationary bike. During cycling, most people experience a feeling of local fatigue in the thighs and therefore stop the test earlier compared to exercising on a treadmill [51]. Moreover, due to the higher grade of exertion on the treadmill compared to cycling, treadmill walking/running has a greater ability to detect coronary artery disease [136]. The patients were taking their usual medications at all tests as recommended by the American College of Sports Medicine [137].

In both paper II and III, we used an individualized ramp protocol, adjusted to last 8-12 minutes [138]. The subjects walked at a predefined speed and the incline of the treadmill was raised 1-2% every, or every second minute. For subjects who were capable of running the inclination was held constant and the speed was increased by 0.5 km/h every, or every second minute. If it seemed like the test would be shorter or longer than the advised time, the protocol was individually adjusted. Reasons to stop were subjective exhaustion or standard clinical criteria [60]. Subjective perception of exertion was assessed immediately after termination using the Borg CR10 scale in paper II and the Borg 6-20 scale in study III [139]. We used the Borg scale that was in clinical use at the rehabilitation centre and the hospitals, and therefore we ended up with two different scales in paper II and III.

Heart rate recovery

HR recovery was defined as the change in HR from peak exercise to one minute after peak exercise with the patient standing still on the treadmill. Some researchers recommend to record HR recovery both at one and two minutes [140] and others look at the whole slope of the HR recovery curve [141]. We chose to use a simple, but still valid, measure of HR recovery because we were several test leaders at the centres, and

therefore assumed that a more advanced protocol would give more sources of error. Also, HR recovery at one minute has proven to be a powerful predictor of all-cause mortality in subjects referred for exercise testing [100, 142].

Work economy

Oxygen uptake in mL· kg^{-1}· min^{-1}at a sub-maximal work load is taken as a reflection of work economy [143]. Before the maximal exercise test in paper II, each subject was tested on sub-maximal, individualized speed and at zero inclination on the treadmill. The work rate for each subject was identical at all testing points. We chose to individualize the work load to be sure that it would be a truly sub-maximal load for all patients, and since the motive for this measurement was intra-individual comparison.

Resting and maximal heart rate

Resting HR was measured using electrocardiography during the ultrasound assessments (echocardiographic recordings in paper II and flow-mediated dilatation in paper III). The subjects rested on an examination bench for minimum 10 minutes before the recordings. Maximal HR was established from the exercise tests. In paper II we reported the maximal HR obtained in the test as the maximum. For a person to reach his individual maximum HR requires however several repeated intervals of maximum effort. The HR at the end of an exercise test is therefore not equal to an individual's maximum HR. Thus, based on practical experience, we added five beats to the HR at peak exercise to get the maximum HR in paper III.

Left ventricular function by echocardiography

Ultrasound investigation of the heart (echocardiography) plays a central role in the evaluation of left ventricular diastolic and systolic function, and different techniques give information on blood flow velocities, myocardial velocities and deformation of the myocardial tissue itself. Echocardiography was used in paper II to investigate cardiac volumes, systolic, and diastolic function. The most commonly used methods to study diastolic function and left ventricular relaxation are variables derived from Doppler mitral blood inflow velocity; the velocities of early (E) and late (A) diastolic mitral flow,

the deceleration time of E (DT) and the ratio of early diastolic to late diastolic flow velocity (E/A). These blood flow velocities were recorded with pulsed wave Doppler-imaging [144]. Also Tissue Doppler imaging, a relatively new echocardiographic technique, was used to measure the velocity of the myocardial motion. An advantage of Tissue Doppler imaging is that the tissue velocities are less load-dependent than measurements of blood velocities [145].

Left ventricular diastolic dysfunction was classified in four groups; impaired relaxation (defined as E/A < 1, or E/A 1-2 and DT > 240 ms), restrictive filling pattern (defined as E/A > 2 or E/A 1-2 and DT < 140 ms) and pseudonormal filling pattern (defined as E/A 1-2, DT 140-240 ms and E'/A' <1). The remaining subjects were classified as normal [80].

Endothelial function

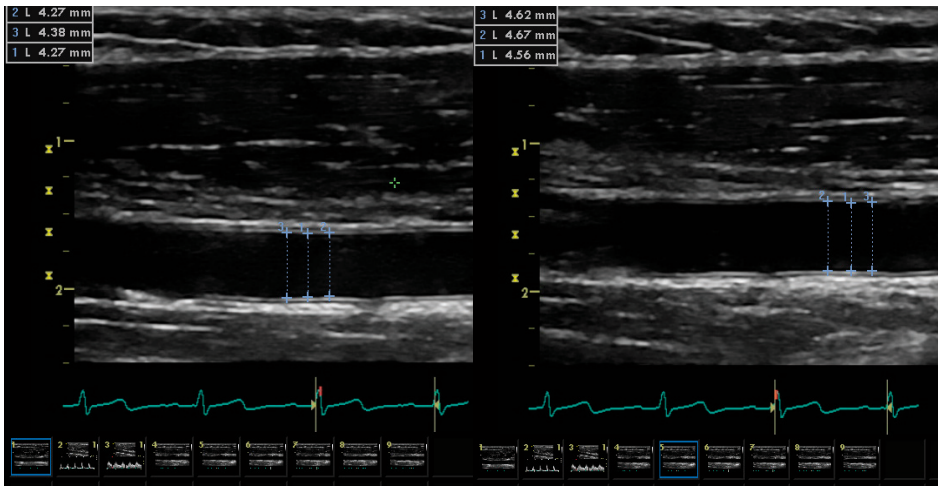
Endothelial function was measured by brachial flow mediated dilatation (FMD) in paper III. The optimal methodology for FMD investigation is still under debate [146], and some of the points of disagreements are considered below. Firstly, there has been some discussion in the literature regarding the placement of the cuff when measuring FMD [147], and the most updated guidelines now recommend distal (below the elbow) placement of the cuff [146, 148] to reflect the NO-mediated dilatation more accurately. Paper III of this thesis was however planned based on the guidelines by Corretti et al [149], and we therefore chose a proximal placement of the cuff. The main objection against a proximal occlusion, is that the dilatation in response is not solely NO mediated [147]. However, there has been documented a close association between angiographically evident CHD and FMD using a proximal occlusion [85]. Further, in several studies demonstrating a prognostic significance of endothelial function, the cuff was placed on the upper arm [87, 88, 150, 151].

In paper III, lumen diameters of arteria brachialis were measured at three consecutive R-waves at baseline and after cuff release, and we used the average on each time point as the diameter. FMD was then calculated as the percent change in diameter compared to baseline. Based on experience in our lab, maximal dilatation is observed one minute after cuff release and therefore we analysed only at that point in time.

The magnitude of FMD is dependent on the stimulus imposed, that is the magnitude of the shear stress in the vessel, and therefore some advocate a normalisation

of the FMD response to the shear rate [148]. We used both non-normalised values and values normalised for peak shear rate, and saw no difference in results between the two. It is also suggested to adjust to the shear rate area under the curve, but at the time of the recordings this normalisation method was not yet published [152]. In fact, there still is disagreement about whether to normalise or not, and large between-subject variations have been seen in the relationship between FMD and shear rate [153, 154].

All measurements of FMD in our study were obtained in a quiet room and after at least 10 hours of fasting and abstinence form caffeine and alcohol. The patients were also asked to restrain from strenuous physical activity for at least 24 hours before the data collection.



A **B**

d = (4.27+4.38+4.27)mm/3 = 4.31 mm **d = (4.62+4.67+4.56)mm/3 = 4.62 mm**

Figure 1. Blood vessel diameter (d) at baseline (A) and after deflation of the cuff (B).
Flow mediated dilatation (FMD) is here calculated to be: $\frac{(4.62-4.31) \times 100}{4.31} = 7.2\%$

Blood analyses

In addition to the blood analyses provided by the rehabilitation centre or hospital laboratories, adiponectin was measured in paper II and III by enzyme-linked immunosorbent assay (ELISA, Mercodia, Uppsala, Sweden). The analysis is based on a technique in which two antibodies are directed against separate antigenic determinants

on the adiponectin molecule (sandwich-technique). This assay measures the level of total adiponectin in the serum or plasma. Although there are indications in the literature for particular importance of high molecular weight adiponectin for vascular-protective activity, the functional role of the different molecular forms of adiponectin remains to be elucidated [108, 155].

Quality of life

There are both generic and disease specific questionnaires on quality of life. In paper II and III, we chose to use the MacNew Heart Disease Health-related Quality of Life (MacNew) Questionnaire since it was designed to evaluate how daily activities and physical, emotional, and social functioning are affected by CHD and its treatment. The MacNew consists of 27 items which fall into three domains; an emotional, a social and a physical domain. The minimum score (low quality of life) in each domain is one and the maximum score is seven. The time frame for the MacNew is the previous two weeks, and it takes in average maximum ten minutes to complete the questionnaire for the subjects [156].

The validity, reliability, responsiveness, and interpretability, of the MacNew have been established. Overall the MacNew has been found to be reliable in that it meets a reproducibility standard of 0.70 for group comparison which usually is the goal in clinical trials [157]. Also different aspects of validity of the MacNew have been confirmed [156], although it is difficult to establish the criterion-related validity in the absence of a widely accepted criterion measure (gold standard) [157]. How sensitive a test is to change is called responsiveness, and the MacNew is found to be responsive and sensitive to change in quality of life following various interventions for CHD patients [156]. Also the interpretability of the MacNew, or the understanding of the meaning of the instrument's quantitative scores, has been found to be good. Dixon et al [158] have investigated the minimal important difference, which is the smallest difference in scores which subjects perceive as beneficial, and found this to be 0.5 in all three domains of MacNew. The validity and reliability of the Norwegian version of MacNew have recently been tested and found to be satisfactory [159].

Training intervention

As exercising with high intensity gives larger increase in VO_{2max}, we wanted to use a model of high intensity aerobic training in paper II and III. Previously our research group has used an exercise model with 4 times 4 minutes of high intensity aerobic interval training (AIT) and found large increases in VO_{2max} in subjects with the metabolic syndrome [47], CHD [45], and heart failure [46] (Figure 2). The same protocol was therefore chosen. In paper II we investigated if AIT could improve VO_{2peak} more than moderate continuous training (MCT) in CABG patients. The MCT chosen was isocaloric to the AIT [45] and therefore potential differences between the two would be attributed to the intensity. In comparison with the earlier studies mentioned, the intervention period in paper II was short; only four weeks. One aim was therefore to investigate if AIT could prove to be superior to MCT even after such a limited time.

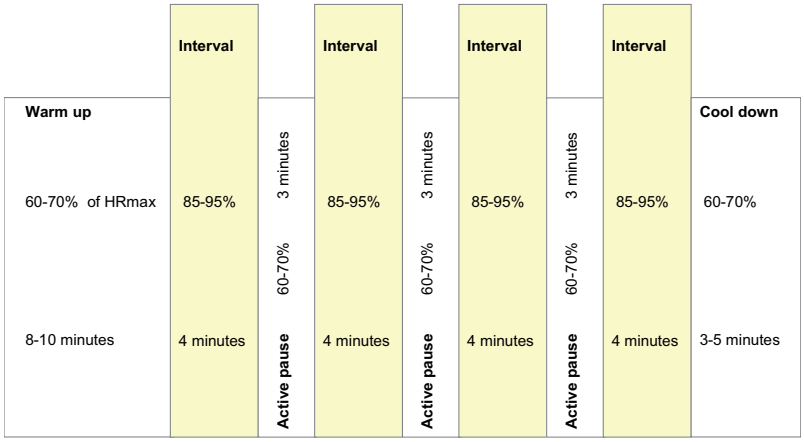


Figure 2. Aerobic interval training (AIT) model used in paper II and III.
HRmax = maximum heart rate.

In paper III we wanted to investigate the effect of the exercise training offered to MI patients at three Norwegian hospitals as usual care. Subjects recovering from MI are often offered to participate in group exercise training at the hospital for a certain period. The short- and long-term effects of these programs have not been extensively studied. We wanted to compare the cardiovascular effects of the existing programs with treadmill AIT. Due to the earlier mentioned studies on the superiority of AIT, interval training

with high intensity has become more incorporated in the clinical field of cardiac rehabilitation in Norway, and physiotherapists try to organise their exercise training according to this model. However, the exact intensity of the group exercise training was unknown.

Exercise training and ß-blockers

Beta-adrenergic blocking agents (ß-blockers) work by blocking the effects of the hormone adrenaline. The patients will thereby have lower HR during exercise than without this medication. Almost all subjects in paper II and III were taking ß-blockers. We used % of maximum (ß-blocked) HR to calculated the target HR for the exercise in AIT in paper II and III and for MCT in paper II [160]. If the patients got their ß-blocker dosage changed during the studies, we calculated a new target HR based on the work load that they had the previous training session. In practice, we used the same speed and inclination and saw what HR this gave and used this new HR as the target for the exercise trainings to follow.

Statistics

Cox regression analysis

In **paper I** we used the Cox proportional hazards model [161] to examine the association between physical activity and mortality in CHD subjects. This model is quite popular in medical research on prospective follow-up data, and is also regarded as mathematically robust. The proportional hazard method is a regression analysis that computes hazard ratios (i.e. relative risks) of the disease by comparing the risk of disease in each category of a predictor variable with the risk in a chosen reference category. The analysis takes individual time at risk into account, and study factors may be entered both as categorical and as continuous variables in the regression model. The Cox model gives the opportunity to control for variables with a potentially confounding effect on the investigated association. Such confounding factors are associated with the exposure and independently affects the risk [162]. In paper I we first performed analyses adjusting only for age, and then also multivariate analyses including other potentially confounding

variables in addition to age. There are other possible regression models to use in survival analysis, but due to its robustness, it is considered as "safe" to use the Cox model when in doubt about what is the correct model to choose [163].

Linear mixed model

Although repeated measures data traditionally have been analysed by repeated measures analysis of variance (ANOVA), newer mixed effects models are considered to be a superior alternative [164]. A linear mixed model was therefore chosen in the analysis of the repeated measures data in paper II. The advantages of these models are that they can account for several sources of random error in the data, such as individual responses and error of measurement. Also, these models use all available data and subjects with missing values do not need to be deleted, as they have to when using repeated measures ANOVA. If the data is missing (completely) at random, the mixed models are valid and fully efficient. It is often difficult to ascertain if drop-outs are random. Often, subjects who do not improve are more likely to drop out of a study. In paper II it was assumed a random drop-out, and we attempted to check for this by comparing outcome data in the drop-outs with data from the whole sample. Based on this, linear mixed models are argued to be an appropriate choice in clinical studies with a relatively long follow-up time [164].

Analysis of covariance

In paper III we analysed changes in outcome variables by analysis of covariace (ANCOVA). ANCOVA is in fact a regression method that relates outcome scores to baseline scores in each of the groups, and thereby adjust each patients follow up score for his or her baseline score [165]. The advantage of this model above comparing change scores by independent t-tests is that it controls for baseline imbalance between the groups.

Summary of results and discussion

Physical activity and mortality in subjects with coronary heart disease (paper I)

In paper I, we found a significant decrease in both cardiovascular and all-cause mortality in subjects who were physically active compared to the reference group (no activity). Interestingly, we saw that exercising only once weekly was associated with significant reduction in mortality with a relative risk of 0.79 (95% confidence interval (CI) 0.65-0.96) for men and 0.69 (95% CI 0.54-0.88) for women. However, we also saw a significant trend ($p<0.001$) for greater reductions with increasing frequency and duration of exercise. Exercising for 15-30 minutes, but not less than 15 minutes, each time was associated with lower mortality. In line with our a priori believes we saw that exercising with moderate/high intensity gave greater reductions in mortality than exercising with low intensity. The difference between low and moderate/high intensity was approximately 10% for all-cause mortality. The results were similar for men and women, and also for all-cause and cardiovascular mortality.

Exercise intensity and mortality

Also some previous epidemiological studies have found positive associations between physical activity and longevity in coronary heart disease (CHD) patients [23-26, 29]. Only a few of the earlier studies have however been able to split the subjects into more than two activity groups, i.e. active versus sedentary, due to restricted number of participants. When studying active versus sedentary, both Steffen-Batey et al [25] and Al-Khalili et al [23] found lower mortality in the active groups. Batty et al [29] used three categories; inactive, moderately active, and active, but ended up with a small statistical power due to few subjects in each group. They found no statistical significant risk reduction in active subjects; in fact, they found an elevated risk in asymptomatic men with a positive exercise electrocardiography at baseline who reported to be active. Some studies have investigated the associations of exercise intensity and mortality. In elderly CHD subjects, neither Janssen and Jolliffe [27] nor Wannamethee et al [24] found additional effects of high intensity physical activity on mortality risk. Actually, the latter of these

found a slightly increased mortality in elderly male CHD patients who reported to be vigorously active compared to the light and moderately active men. These studies are therefore not in line with the results of paper I, where we found larger mortality reductions with moderate/high intensity exercise in CHD subject. One important difference between the study by Wannamethee et al [24] and our, was that they used absolute intensity while we used relative intensity. As physiological adaptations to exercise are more dependent on the relative intensity in relation to the individuals own maximum than to the absolute intensity [166], the use of relative intensity is considered as a strength of our study. In subjects with CHD, low absolute levels of physical activity will elicit high relative intensity due to reduced physical capacity. When comparing subjects at different fitness levels, there is a great difference in the relative intensity of a common task as walking 6 km/h. For a top athlete this will be low intensity, while for many CHD patients it will be at or above their maximal capacity.

The newest recommendation for physical activity in adults defines aerobic intensity in absolute terms, e.g., moderate intensity comprises 3.0-6.0 metabolic equivalents (METS) [21]. Also, 6 METS is a threshold often used in epidemiological studies to indicate vigorous activity. As outlined above, it can be argued that this threshold is arbitrary since exercising at < 6 METS for subjects with low exercise capacity may elicit physiological responses associated with high intensity exercise, i.e. large myocardial oxygen demands [126]. The current recommendation on physical activity in older adults is in fact more appropriate since it defines intensity in relative terms [167]. Given the heterogeneity of fitness level among CHD patient, recommendations on physical activity should be on a relative scale. Of note, relative intensity has proven superior to absolute intensity in predicting CHD risk [166].

Whether vigorous physical activity adds to the effects of moderate intensity activity in a public health perspective has been debated [4, 135, 168, 169]. This uncertainty is also reflected in the guidelines on physical activity given through the years [170, 171] [172]. The updated ACSM recommendation for physical activity and public health for adults now advice activity with moderate intensity for a minimum of 30 minutes on five days or vigorous intensity for a minimum of 20 minutes on three days each week [21].

Minimal and optimal amount of exercise for longevity

Minimal adherence to public health guidelines [21] on physical activity requires an energy expenditure of about 1000 kcal/week. In some studies, both regarding healthy subjects [4, 169] and CHD patients [27] physical activity levels below this energy expenditure associate with significant reductions in mortality risk. This was also found in paper I. Therefore, it may be important to acknowledge all physical activity as health promoting for CHD patients. At the same time, we also found significantly decreased mortality risk with larger amounts (both duration and frequency $p \leq 0.001$ for trend) of exercise. When recommending physical activity to the general population, or to the CHD subgroup, one should aim at getting as many as possible to do sufficient exercise for health benefits. Recommending too large dosages of activity may make some people find the recommendations unattainable and thereby refrain from exercising at all. Also, if recommending smaller dosages than today, there will be the risk of not achieving the health benefits. It should therefore be emphasised that doing a little exercise is good, but doing more is better.

Physical activity and physical capacity in CHD patients

The question whether physical activity or capacity is the most important factor for survival is not fully settled. Regarding cardiovascular risk factors, Sassen et al [173] found greater effects of physical capacity than activity, and actually no significant effect of total hours of physical activity or low/moderate intensity activity. Unfortunately, we do not have data on the subject's level of physical fitness in our HUNT-study. Although the correlation between the reported physical activity level in the HUNT questionnaire and VO_{2max} has been reported to be as good as in other physical activity questionnaires [174], there is still only a modest correlation. Therefore, we can not conclude about physical capacity and mortality based on the results in paper I. The risk reduction associated with physical activity seen in paper I was similar as in meta-analyses on the effect of exercise training/rehabilitation programs for CHD patients (20-30%) [55-57]. Interestingly, 44% of the CHD patients reported to exercise 2 times per week or more, compared to only 24% in the subjects without CHD in the same population [4].

Randomised clinical trials of aerobic interval training in CHD patients (paper II and III)

As exercise capacity is a strong predictor of mortality in CHD patients [7, 34], one should aim at finding optimal exercise protocols for increasing peak oxygen uptake (VO_{2peak}) in these patients through randomised clinical trials. In addition, there are indications that being fit is even more important than being physically active *per se* in controlling cardiovascular risk factors [173]. In paper II we found significantly increased VO_{2peak} after both aerobic interval training (AIT) and moderate continuous training in coronary artery bypass surgery (CABG) patients after four weeks at a rehabilitation centre. In contrast to our hypothesis that AIT would increase VO_{2peak} more than moderate continuous training (MCT), we found no significant difference between the two training programs after four weeks. At the follow-up test six months after leaving the centre, we saw however significantly increased VO_{2peak} only in the AIT group. Quality of life, heart rate (HR) recovery, and work economy increased significantly, and resting HR decreased significantly, in both groups after four weeks (non-significant between-group difference). At the follow-up test we saw no major changes in these secondary outcome measures compared to discharge. We did not find significant changes in traditional circulating biomarkers of cardiovascular disease or in adiponectin levels. At the follow-up test after six months, adiponectin levels had decreased significantly in both groups (non-significant between-group difference). We saw no significant changes in left ventricular function after the exercise training period.

In paper III, MI patients referred to exercise training at three Norwegian hospitals had a superior effect of treadmill AIT on VO_{2peak} compared to the usual care group exercise programs. In the eight minutes with the highest intensity of each session, the treadmill AIT patients exercised with higher intensity than the patients attending group exercise, even though the hospitals aimed at reaching high intensity during the group exercise (Figure 3). Changes in quality of life, endothelial function, HR recovery, resting HR, and blood markers of cardiovascular disease were similar after treadmill AIT and group exercise.

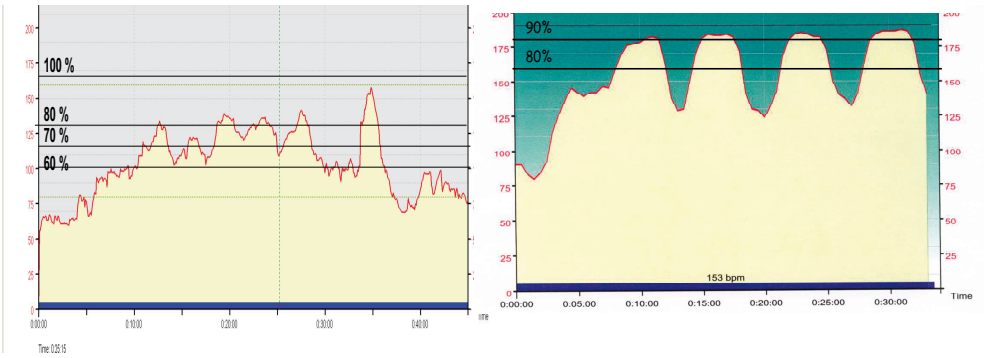


Figure 3. Heart rate curves from two patients in paper III. The left illustration (A) is a patient in group exercise and the right illustration (B) is a patient in treadmill aerobic interval training.

Changes is VO_{2peak}

In paper II, we saw a trend towards greater increase in VO_{2peak} after AIT compared to MCT after the four weeks at the rehabilitation centre (group*time interaction, p=0.19). Probably, the relatively short training intervention period was not sufficient to give larger effect of AIT compared to MCT. Another possible explanation for the lack of difference between the groups was that all patients also participated in the regular exercise program at the rehabilitation centre. This program consisted of a variety of exercise training, both with high and moderate intensity. In total the patients did a lot of exercise training during these four weeks. Maybe some of them, especially in the AIT group, experienced an overload of training and therefore did not increase VO_{2peak} optimally. The further increase in VO_{2peak} seen at the follow-up test in the AIT group was presumably due to more high intensity training at home. According to their training diaries, half of the AIT patients were doing moderate/high intensity exercise training more than three times per week, while only one of the MCT patients reported this. Some of the apparent increase in VO_{2peak} from discharge (4 weeks) to follow-up (6 months) may also be due to the fact that we tested the patients shortly after the last exercise session at discharge. This would possibly mask some of the training effect at four weeks and give a VO_{2peak} that was actually lower than if we had tested them some days later, allowing a super-compensation to occur.

Although the intention was high intensity AIT also in the comparison group (usual care group exercise) in paper III, we saw larger increase in VO_{2peak} after treadmill AIT compared to group exercise. The most likely explanation for the greater increase in VO_{2peak} after treadmill AIT, was the higher relative exercise intensity in this group (90% versus 81% of HR maximum in treadmill AIT and group exercise, respectively). Probably it is not the average intensity of an exercise session that is most important for improvements in VO_{2peak}, rather the intensity in the periods with high intensity (intervals).

The increase in VO_{2peak} divided by the number of AIT exercise sessions was similar in paper II and paper III (Figure 4). The changes were also in line with two other studies on the effect of AIT in CHD patients [45, 175]. In the study by Rognmo et al [45], VO_{2peak} increased by 0.21 mL· kg · min^{-1} (0.63%) per training session, and in paper II and III the changes were 0.20 mL· kg · min^{-1} (0.74%) and 0.22 mL· kg · min^{-1} (0.66%), respectively. The number of exercise sessions varied between the studies, with 28.3 AIT sessions in Rognmo et al [45], 16.4 in paper II, and 20.4 in paper III. After 12 weeks of AIT in post MI heart failure patients, Wisløff et al [46] found an average increase in VO_{2peak} per exercise session of 0.16 mL· kg · min^{-1}. In relative means, this increase was in fact 1.19% per session. In moderately trained healthy subjects, an absolute increase in VO_{2peak} per exercise session of 0.22 mL· kg · min^{-1} has been reported [43]. Hence, the CHD patients in paper II and III had similar increase in VO_{2peak} per exercise session as healthy subjects doing AIT.

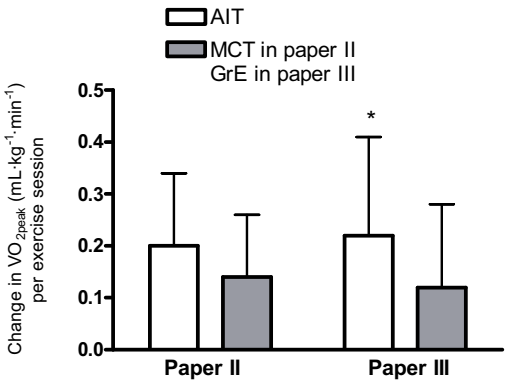


Figure 4. Changes in VO_{2peak} per exercise session, calculated as total change in VO_{2peak} divided by the number of exercise session per patient. AIT = aerobic interval training MCT = moderate continuous training GrE =group exercise training.

* indicate significant difference between groups in paper III ($p < 0.01$).

As we know that exercise capacity is a strong predictor of mortality in cardiac patients [7, 34], it is tempting to conclude that the increase in VO_{2peak} seen in paper II and III will have prognostic significance for these patients. However, our studies were not designed to test this, rather, to investigate the changes in VO_{2peak} with different exercise training protocols. The potential of an increase in VO_{2peak} to improve the prognosis in CHD patients remains to be demonstrated and this will require a large, multicentre trial. In the meanwhile we have to rely on the meta-analyses [55-57].

Of interest, we see that the exercise amount and intensity used in paper III, correspond to the exercise amount and intensity associated with the largest risk reduction in paper I. Exercise training 1-3 times per week with duration of more than 30 minutes and moderate/high intensity was associated with a 40% reduction in mortality for men and women combined. Again, the actual effect of exercise training on mortality for subjects with CHD remains to be studied in randomised controlled trials.

Heart rate recovery

In paper II we found a significant increase in HR recovery after four weeks of both AIT and MCT (non-significant group-difference), with no significant changes between four weeks and six months follow-up. In the absence of a cool-down period, a cut-off value of ≤ 18 beats/min has been considered abnormal and predictive of death [98]. In paper II, 13 of the patients in AIT and ten of the patients in MCT had a HR recovery below this value before the training period. The numbers were reduced to seven in each group after four weeks and to four and six at the follow-up after six months in the AIT and MCT groups, respectively (Figure 5). It can be argued that the increase in HR recovery seen was due to spontaneous recovery after the bypass surgery, however, others have found HR recovery to be virtually unchanged in CABG patients who did not exercise [74]. Also, increased HR recovery has been found in chronic angina pectoris patients after a period of exercise training [176].

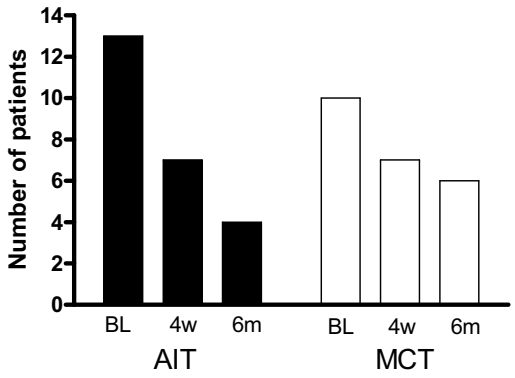


Figure 5. Number of patients in paper II with a heart rate recovery ≤18 beats/min.
BL = baseline
4w = at discharge from the rehabilitation centre
6m = six months follow-up
AIT = aerobic interval training
MCT = moderate continuous training

In contrast to the results in paper II, HR recovery of the MI patients in paper III did not increase significantly after the training period. Gialluria et al [70] found increased HR recovery in MI patients after 12 weeks of exercise training. The reason for this difference in response is presently not known. The patients included in paper III were quite fit MI patients with a HR recovery at baseline of 32.2 (± 9.6) beats/min, and a possible explanation for no change could therefore be that they already had a HR recovery close to normal at baseline. Only six subjects had a value ≤ 18 beats/min before the training period in paper III (reduced to four subjects after the training period). In comparison, the baseline HR recovery in Gialluria et al [70] was 17.1 (±1.8) and 18.8 (± 2.1) beats/min in the two training groups, respectively.

Circulating biomarkers of CHD

We saw no major changes in traditional circulating biomarkers of CHD (such as total and high-density lipoprotein (HDL) cholesterol) in either paper II or III. This is in line with Kim et al [177] who reported no significant changes in total cholesterol, HDL, low-density lipoprotein cholesterol or triglycerides after 6 months of exercise training in CHD patients. We did however find significant increases in adiponectin, a recently emerged cytokine with anti-atherosclerotic properties produced in the adipose tissue, in both papers [105]. In paper II, adiponectin increased between the test at the end of the training period at the rehabilitation centre (4w) and the follow-up test (6m) in both the AIT and MCT groups (non-significant between-group difference). Also in paper III, adiponectin increased after both group exercise and treadmill AIT (non-significant

between-group difference). Changes in adioponectin after exercise training have not been studied extensively in CHD patients. Previous studies have reported of increased levels of circulating adiponectin after exercise training in subjects with conditions related to CHD, like the metabolic syndrome [47], type 2 diabetes [178, 179] and obesity [114], although the data are not consistent [115].

In both paper II and III, serum ferritin decreased significantly after exercise training in all groups. This was unexpected, and we have to look at these changes as hypothesis-generating for further studies. Increased ferritin levels have been linked to incidence of CHD, but the relationship is not fully understood and not consistent in all studies (for a review, see You et al [180]). Of interest, both adiponectin and ferritin were recently shown to be part of a new model for predicting development of type 2 diabetes [181].

Quality of life

Quality of life increased significantly in paper II and III after the exercise training period. In paper II, we saw that the improvement was sustained at six months follow-up. All domains of the MacNew Heart Disease Health-related Quality of Life Questionnaire (MacNew) improved in both studies, indicating that their general quality of life, not just the physical domain, improved. When comparing the results from paper II and III, we see that the changes in quality of life scores after the rehabilitation period are quite similar in the two. The CABG patients in paper II had a lower score in the physical and social domain at baseline than the MI patients in paper III. This is also reflected in their lower VO_{2peak} at baseline. When considering the surgery the CABG patients had prior to the inclusion, this is not so surprising. The similar changes we saw after the training periods in both papers may indicate that exercise training has the potential to increase quality of life in CHD patients with various starting points. In both papers we saw changes in quality of life of magnitudes that have been considered to be clinically important in all domains [158]. The three domains of the MacNew overlap in some extent, since some of the questions in the questionnaire are counted in more than one domain, and this has to be acknowledged in the interpretation of the results. Interestingly, the quality of life of the CHD patients in paper II and III did not differ much from normative data [158]. Actually, they had average values that were equal or higher than the general population at baseline, and still we saw significant, clinically important increases in

quality of life after exercise training. Our results are in line with several previous studies showing improved quality of life after cardiac rehabilitation [63, 120-123].

Left ventricular function

Apart from a decrease in early diastolic mitral flow velocity (E) after AIT, we saw no major changes in left ventricular function in paper II. As E has a non-linear relation to diastolic dysfunction due to its load dependency, early diastolic mitral velocity (e') was considered to be a more robust marker of left ventricular diastolic function. Also the fact that none of the other variables characterising diastolic function changed after exercise made us interpret the change in E with caution. We therefore concluded with no significant changes in either diastolic or systolic function after four weeks of exercise training in CABG patients in paper II. Four weeks may be insufficient to engender alterations in cardiac function, and the contribution of cardiac function to training adaptation may require studies of greater duration [82, 182]. Some previous studies on left ventricular function in CHD patients agree with ours regarding systolic function [80, 183]. Amundsen et al [183] found improved early diastolic myocardial relaxation rate in CHD patients after eight weeks of AIT three times weekly. One could therefore assume that the training period needs to be longer than four weeks to get cardiac adaptations. The increase in VO_{2peak} seen in paper II may therefore be due to noncardiac factors.

Or else, it is possible that cardiac changes could be apparent using echocardiography during work or immediately post exercise. There are examples in the literature of changes in cardiac function after a period of exercise training detectable only when using exercise echocardiography [69, 184].

Flow-mediated dilatation

We found significantly increased flow-mediated dilatation (FMD) after both group exercise training and treadmill AIT in paper III. The optimal intensity, volume, and modality of exercise training for FMD improvements in CHD patients is not yet settled. Earlier studies on heart failure patients [46] and subjects with the metabolic syndrome [47] have reported of larger FMD improvements after AIT compared to moderate continuous exercise. In paper III, we compared AIT with an exercise protocol with a higher

intensity than the comparison groups in the mentioned studies, and this may be the reason for the non-significant difference between the groups.

Clinical implications

The main reason for carrying out paper I-III was to get more knowledge regarding exercise training in CHD patients, and thereby to give scientifically documented recommendations on exercise in these patients. Hopefully the clinical field of cardiac rehabilitation will implement some of our findings. Paper I indicated that the minimal effective dose of physical activity was only 15-30 minutes once weekly for significant reductions in mortality. Also, we found larger reductions associated with moderate/high intensity activity than with low intensity. Both these observations should be communicated to CHD patients, especially patients not attending organised rehabilitation. It is to be hoped that such documentation will motivate the patients to do at least a minimum of exercise. Although we have to be cautious in interpreting the results from an epidemiologic study, we could tell the patients to exercise at least once weekly instead of several times as we told the patients to after the intervention period of paper II and III. However, there will probably be larger reductions in mortality with more exercise. In addition, there are other positive health effects of more frequent exercise.

The patients in paper II and III can be regarded as quite representative for CABG patients at a Norwegian rehabilitation centre and MI patients at Norwegian hospitals. As outlined in the methods section, the MI patients in paper III were younger than MI patients at the cardiac unit at the largest hospital in the study. Therefore it is uncertain whether the conclusions of paper III apply to the general MI patient population. However, others have found no major differences in the responses in exercise capacity to exercise training in CHD patients 45-65 compared to 66-75 years [63]. Although increased exercise capacity has been reported after exercise training also in very old MI patients (>75 years), the increase was lower than in younger patients [63].

The patients in both paper II and III are regarded as relatively fit CHD patients, based on their relatively high initial VO_{2peak}, in comparison with other studies on this patient group. One possible reason for this is that we used treadmills in the exercise testing whereas many others [61, 62, 67, 68, 71, 74, 95] used stationary bikes.

Feasibility of AIT

When inspecting the training diaries from paper II, we saw that 12 out of 23 patients managed to keep on doing AIT as home exercise. In the MCT group, 16 out of 25 reported to exercise > 3 times per week with moderate intensity, and only one patient with high intensity. In advance, we had actually hypothesised that it would be more feasible to do MCT at home and that these patients would adhere better to the prescriptions and thereby increase more in VO_{2peak}. The results showed however that AIT was feasible and that the adherence was as good in this group as in MCT. In addition to the 12 patients in AIT reporting moderate or high intensity > 3 times per week, five reported to exercise > 3 times per week with moderate intensity only. Several of the patients randomised to AIT told us that they found it a bit hard to do AIT, but they experienced that they were getting more fit by doing it. Our impression was that the follow-up test was a motivational factor for carrying out these exercise programs. This is an observation that could have clinical implications as repeated exercise testing could motivate more CHD patients to exercise.

Paper II and III investigated the use of treadmill AIT in clinical settings. A substantial part of the exercise training was lead by physiotherapists without former experience with treadmill AIT, but we experienced no major problems with getting the patients to do this kind of exercise training. The three hospitals in paper III already intended to do AIT organised as group exercise. Our study has however showed that it is not so easy to reach high intensity in group exercise as when using treadmills in CHD patients. Using heart rate monitors more actively and making sure that the patients are exercising at high intensity in periods of the exercise session could make the group exercise as effective as treadmill training for these patients. This remains however to be studied.

Gender aspects

We saw no major gender differences neither in mortality associated with physical activity in the epidemiologic study nor in the effects of exercise training in the clinical studies. However, we saw some differences in the amount and intensity of exercise reported by men and women in paper I. As much as one third of the women reported of no activity, but only 14% of the men reported not to be active. Further, half of the men

and 40% of the women reported to exercise two or more times per week. Also, more men than women reported to do exercise with moderate/high intensity, with 11% and 3% of active men and women, respectively. These data suggest that there is a need to address women in particular when recommending exercise training for CHD patients.

In paper II and III we wanted to include both men and women, but in practice we experienced that women were excluded more often than men due to co-morbidity giving physical limitations. One explanation for this could be that women in average get CHD at a higher age than men. Also studies included in meta-analyses are most often based on data on men only; actually Taylor et al [56] reported that although women were included in about half of the studies, they constituted only 20% of the patients. Furthermore, there is still published only a few epidemiological studies on the association between physical activity and mortality including women with CHD [23, 25]. Although women were included by Steffen-Batey et al [25], their analyses were done on both genders together. Al-Khalili et al [23] included only women below 66 years so their population was different from our. Generally, these and our study show the same benefit of physical activity for CHD women as for men, with a tendency to even greater mortality reductions among women compared to men in our study (tables 2-4 in paper I).

Ethical considerations

All three study protocols in this thesis were approved by the regional ethical committee. To study the effects of exercise training in CHD patients, it would have been interesting to have control groups who were advised not to do exercise in paper II and III. This was however considered to be unethical due to the well documented benefits of exercise for these patients [55-58, 61-63, 69, 71, 74].

Safety of AIT

Currently there is little information on the safety of high intensity aerobic training in CHD patients. However, in our research group we have carried out several studies using the AIT model, and so far counted ~2800 uncomplicated exercise bouts of AIT in CHD patients [45, 46, 175] (+ paper II, III, and unpublished data). Also other research groups have carried out AIT in CHD patients without reporting serious adverse events [71, 73]. There clearly is a need for further investigating the safety aspect of AIT in CHD patients.

Limitations

Some study limitations are acknowledged. Several of the participants in paper I have probably changed their level of physical activity since the baseline data collection in 1984-1986. As mortality rate reductions are more associated with recent activity than past activity [185], this would probably underestimate the true difference in survival between the physically active and sedentary subjects [186]. In epidemiologic studies there will always be difficult to establish unbiased cause-effect relationships. To try to avoid reversed causation, we also performed the analyses with adjustment for disability status. We then saw only minor changes in the results, indicating that the disease severity in the sedentary group was not the reason for higher mortality rates. Due to the limited number of patients reporting to get exhausted when exercising, we had to merge the sweat and exhausted categories of intensity into one to get more statistical power. This weakened our possibility to examine the effect of high intensity exercise.

There are some possible limitations to paper II as well. The most striking one being the additional exercise training performed by both groups when staying at the rehabilitation centre. This was recognised in advance of the study, but we though it would be hard to recruit patients to just walking on treadmills for four weeks when they were at a rehabilitation centre fully equipped for all kinds of activities. To minimize the bias introduced by the additional exercise training, we could have asked the patients to exercise according to the intensity zones prescribed in the study protocol also in the additional exercise session. Another limitation in this study was that we did only record resting echocardiography and not during or immediately post exercise. Left ventricular changes may have been detectable if we could have used exercise echocardiography as indicated by others [69, 184]. Also, the study would have been better if we had gotten more detailed training diaries from all subjects or had objectively measured physical activity in the follow-up period.

In paper III we experienced some difficulties in carrying out a study in three different hospitals. This resulted in different protocols used in measuring work economy, FMD and also in registering excluded subjects. Data on work economy and excluded subjects are therefore not reported in paper III, and FMD data are reported only from two of the hospitals. Also, it would be nice to have a better registration of the amount and intensity of the home exercise training of the subjects as they were advised

to exercise once weekly on their own during the study period. In paper III we report only results from before and after the training period, with no follow-up data, and this is regarded as a limitation.

Conclusions

Using data from a prospective, population-based cohort study (Nord-Trøndelag Health Study, HUNT-1), we found physical activity to be associated with decreased mortality in subjects with coronary heart disease. Exercising once weekly for 15-30 minutes was found to be enough to reduce both cardiovascular mortality and all-cause mortality in both men and women. Moderate or high exercise intensity was associated with approximately 10% lower mortality risk compared to low intensity.

Peak oxygen uptake (VO_{2peak}), heart rate (HR) recovery and quality of life increased significantly after four weeks of both aerobic interval training (AIT) and moderate continuous exercise training (MCT) in coronary artery bypass surgery patients. At the follow-up testing six months later, AIT had a superior increase in VO_{2peak} compared to MCT.

VO_{2peak} increased significantly more after 12 weeks of AIT versus the group exercise training offered to myocardial infarction (MI) patients as usual care by three Norwegian hospitals. The exercise intensity was significantly higher in AIT compared to the group exercise training, indicating an importance of exercise intensity for improvements in VO_{2peak} after MI.

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Paper I

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Paper II

Aerobic interval training versus continuous moderate exercise after coronary artery bypass surgery: A randomized study of cardiovascular effects and quality of life

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Background Peak oxygen uptake (Vo_{2peak}) strongly predicts mortality in cardiac patients. We compared the effects of aerobic interval training (AIT) versus moderate continuous training (MCT) on Vo_{2peak} and quality of life after coronary artery bypass grafting (CABG).

Methods Fifty-nine CABG patients were randomized to either AIT at 90% of maximum heart rate or MCT at 70% of maximum heart rate, 5 d/wk, for 4 weeks at a rehabilitation center. Primary outcome was Vo_{2peak}, at baseline, after rehabilitation (4 weeks), and after 6 months of home-based exercise (6 months).

Results Vo_{2peak} increased between baseline and 4 weeks in AIT (27.1 ± 4.5 vs 30.4 ± 5.5 $mL \cdot kg^{-1} \cdot min^{-1}$, $P < .001$) and MCT (26.2 ± 5.2 vs 28.5 ± 5.6 $mL \cdot kg^{-1} \cdot min^{-1}$, $P < .001$; group difference, not significant). Aerobic interval training increased Vo_{2peak} between 4 weeks and 6 months (30.4 ± 5.5 vs 32.2 ± 7.0 $mL \cdot kg^{-1} \cdot min^{-1}$, $P < .001$), with no significant change in MCT (28.5 ± 5.6 vs 29.5 ± 5.7 $mL \cdot kg^{-1} \cdot min^{-1}$). Quality of life improved in both groups from baseline to 4 weeks, remaining improved at 6 months. There were no changes in echocardiographic systolic and diastolic left ventricular function. Adiponectin increased between 4 weeks and 6 months in both groups (group differences, not significant).

Conclusions Four weeks of intense training increased Vo_{2peak} significantly after both AIT and MCT. Six months later, the AIT group had a significantly higher Vo_{2peak} than MCT. The results indicate that AIT and MCT increase Vo_{2peak} similarly in the short term, but with better long-term effect of AIT after CABG. (Am Heart J 2009;158:1031-7.)

Many patients are enrolled in cardiac rehabilitation programs after coronary artery bypass grafting (CABG). A recent meta-analysis indicated that such programs reduce total and cardiac mortality by 20% to 26% compared to standard medical care.[1] Exercise capacity has been shown to be the best predictor of survival, both in healthy individuals and in subjects with cardiovascular disease.[2,3] Despite exercise training having become a central element of cardiac rehabilitation, the best way to structure the exercise with respect to amount, mode, frequency, and intensity is still unknown. Aerobic interval training (AIT) has been shown to improve cardiovascular function more than moderate continuous training (MCT) in patients with angina pectoris,[4] metabolic syndrome,[5] heart failure,[6] and also in healthy subjects.[7] In these studies, the training period has lasted 8–16 weeks. Some patients, however, are offered to stay at residential rehabilitation centers for shorter periods, undergoing more intense training programs.

This randomized controlled study aimed to investigate the effect of AIT versus MCT on peak oxygen uptake (Vo_{2peak}) in CABG patients staying at a rehabilitation center for 4 weeks. We hypothesized that AIT would increase Vo_{2peak} more than MCT and that there would no longer be a difference between them after 6 months' home exercise because of insufficient exercise training in both groups. Secondary outcome measures were left ventricular function, heart rate recovery (HR recovery),

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resting heart rate (HR), work economy, quality of life, and blood markers of cardiovascular disease.

Methods

Patients

Coronary artery bypass grafting patients referred to a residential rehabilitation center 4 to 16 weeks postoperatively were included. Exclusion criteria were heart failure, inability to exercise, or drug abuse.

Exercise training

The aerobic exercise training program consisted of treadmill walking, 5 days a week for 4 weeks. Patients were randomized to either AIT or MCT. Aerobic interval training consisted of 8 minutes warm-up, followed by 4 times of 4-minute intervals with HR at 90% of maximum HR, with active pauses of 3 minutes of walking at 70% of maximum HR. The exercise session was terminated by 5 minutes cool-down. The MCT group walked continuously at 70% of maximum HR for 46 minutes to ensure isoenergetic training protocols.[4] The intensity was controlled by HR monitors (Polar Electro, Kempele, Finland) and the patients also reported their perceived exertion according to the Borg CR10 scale.[8] In addition, patients participated in ordinary training sessions at the rehabilitation center consisting of a variety of exercise modes and intensities, of 45 to 60 minutes duration. This additional exercise training was identical in both groups. The exact intensity of 58 such sessions was measured by making a subset of patients wear HR monitors.

At discharge from the rehabilitation center, all patients received written advices to exercise at home 3 to 4 times per week with the same intensity and duration as they were randomized to while at the center and a training diary to register their exercise training.

Outcomes

The primary outcome measure was Vo_{2peak}. Secondary outcome measures were left ventricular function, HR recovery, resting HR, work economy, quality of life, and blood markers of cardiovascular disease. We measured these outcomes at 3 time points: at baseline, after 4 weeks of rehabilitation at the center (4w), and at follow-up 6 months after discharge from the center (6m). Left ventricular function, work economy, and resting HR were measured only at baseline and 4w.

Cardiorespiratory measurements. Vo_{2peak} was measured on treadmill. Respiratory gas was analyzed (Oxycon Delta, Jaeger, Hochberg, Germany), and 12-lead electrocardiography was monitored continuously (Cardiosoft GE Medical Systems, Freiburg, Germany). Blood pressure was measured every second minute using an automatic device (Bosotron 2, Bosch & Sohn, Jungingen, Germany).

We used a ramp protocol individually adjusted to last 8 to 12 minutes after warm-up.[9] Maximal HR at the end of the test was set as the individuals' maximum HR. HR recovery was defined as the change in the HR from peak exercise to 1 minute after peak exercise with the patient standing still on the treadmill. Oxygen uptake in milliliters per kilogram per minute at a fixed submaximal work load defined work economy.

Echocardiography. Echocardiography was performed in 38 subjects during supine rest in the left lateral position using a Vivid Five scanner with a 2.5-MHz phased array probe (GE Vingmed Ultrasound, Horten, Norway). Data were stored digitally and analyzed off-line. Mitral annular velocities in systole (S') and early (e') and late (a') diastole were measured by pulsed tissue Doppler images in the septal, lateral, anterior, and posterior points and averaged. Mitral flow velocity (E) was measured by averaging 3 cycles. Ejection fraction (EF), end-diastolic volume, and end-systolic volume were measured by the modified Simpson biplane method. An investigator blinded for group allocation and time of recording analyzed the data.

Blood analyses. Venous blood was drawn after 10 hours of overnight fasting and analyzed by investigators blinded for the subjects' group allocation. We analyzed for high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, sodium, potassium, creatinine, glucose, albumin, ferritin, and hemoglobin using standard local procedures. Adiponectin was measured in plasma using enzyme immunoassay (Mercodia, Uppsala, Sweden) in 23 randomly selected subjects from each group.

Quality of life. Quality of life variables were assessed using the MacNew questionnaire. MacNew has been proved to be a valid, reliable, responsive test and applicable to patients after CABG.[10]

Sample size and randomization procedure

A difference in Vo_{2peak} improvement (from baseline to 4w) of 3.0 $mL \cdot kg^{-1} \cdot min^{-1}$ between the 2 groups was considered clinically important.[3] Given a within-group standard deviation of 4.0, this yields a standardized difference of 0.75. With a 2-tailed t test for independent samples at a power of 0.8 and $\alpha = .05$, a total of 58 subjects had to be enrolled.[11] The actual statistical analysis performed also takes within-person correlation into account, thereby improving power.

Subjects were included after initial assessments, then randomly assigned to either AIT or MCT, stratified by gender. The randomization code was developed using a computer random number generator, by another unit at the university to ensure blinding.

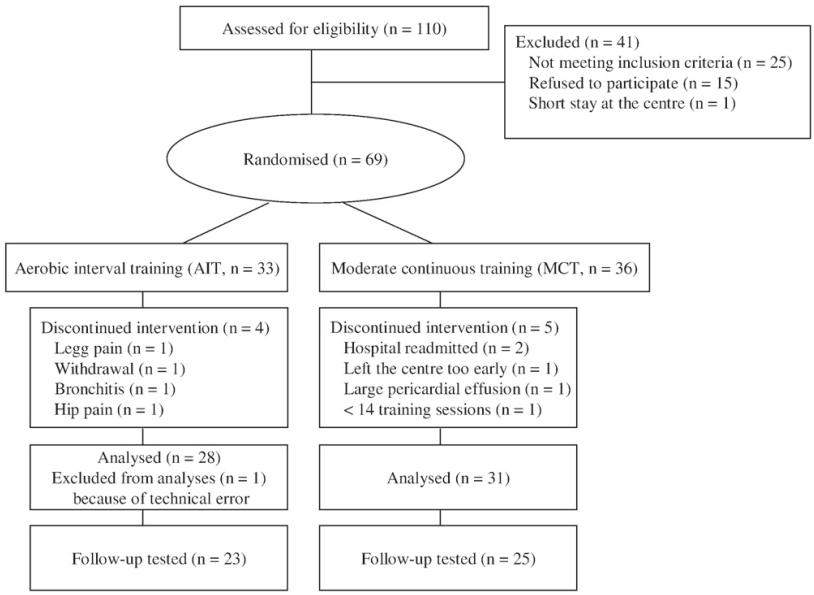
Ethics

The Regional Committee for Medical Research Ethics approved the study, and the study was conducted in accordance with the Declaration of Helsinki. All subjects gave their informed, written consent.

Statistical analysis

To model the outcome variable Vo_{2peak} over time, we used a linear mixed effects model. This allows for observations missing at random, as well as repeated measurements by inclusion of an individual offset as a random effect.[12] Patient age and sex were included as covariates to improve precision. Post hoc comparisons of time points within groups were based on the estimated marginal means and corresponding covariance matrix, using the software R.[13] Other analyses were performed using SPSS for Windows (version 15.0; SPSS, Chicago, IL). To investigate within-group comparisons at different time points of the secondary outcomes, we did paired t tests if a normal distribution could be assumed; otherwise, we used Wilcoxon nonparametric signed rank test. Between-group comparisons of echocardiography variables were done using analysis of

Figure 1



Flow chart of the participants throughout the study.

covariance with the baseline values as covariates. Tests were 2-sided and P values $\leq .05$ were considered significant; no correction for multiple tests was applied.

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Table I. Patient characteristics and medication use at baseline

	AIT (n = 28)	MCT (n = 31)
Age (y)	60.2 (6.9)	62.0 (7.6)
Male/female	24/4	24/7
Days since operation	62 (18)	63 (19)
Body mass index (kg/m^2)	26.0 (6.2)	28.1 (3.5)
Initial Vo_{2peak} mL·kg^{-1}·min^{-1})	27.1 (4.5)	26.2 (5.2)
Type 2 diabetes mellitus (no. of subjects)	4	2
Medications (no. of subjects)		
β-Blockers	27	31
Statins	28	31
Diuretics	3	8
ACE inhibitors	5	7

If not otherwise stated, values are mean ± SD. ACE, Angiotensin-converting enzyme.

Results

Participant flow and protocol deviations

We recruited patients between April 2004 and November 2006 (Figure 1). Baseline characteristics of the 2 groups were well balanced (Table I). There were no major complications or cardiac events during the study period. One patient was excluded after randomization to MCT because of a large pericardial effusion that had not been discovered at the time of allocation. Oxygen uptake data on one patient in the AIT group were excluded from the analysis because of a technical error in the measurement. This patient refused retesting. Only subjects attending ≥14 exercises were included. Two subject in AIT and 3 subjects in MCT changed their β-blocker dosage during the rehabilitation stay, and 5 subjects in AIT and 2 in MCT changed their dosage between 4w and 6 months.

Follow-up testing (6m) was done 27.5 (SD 3.3) and 27.0 (SD 2.7) weeks after 4 weeks in AIT and MCT, respectively. Five patients in AIT and 6 in MCT did not turn up for follow-up testing, for the following reasons: work-related (n = 3), comorbidity (n = 3), refusal (n = 4),

Table II. Cardiorespiratory variables, quality of life, and blood markers at baseline (BL), 4w, and 6m

	AIT			MCT		
	BL (n = 28)	**4w (n = 28)**	**6m (n = 23)**	**BL (n = 31)**	**4w (n = 31)**	**6m (n = 25)**
Maximal exercise test						
Vo_{2peak} (mL · kg^{-1} · min^{-1})	27.1 ± 4.5	30.4 ± 5.5*	32.2 ± 7.0†,‡	26.2 ± 5.2	28.5 ± 5.6*	29.5 ± 6.7
Perceived exertion	8.3 ± 1.5	8.2 ± 1.3	7.9 ± 1.3	8.1 ± 1.5	7.6 ± 1.9	7.1 ± 1.8
RER at Vo_{2peak}	1.13 ± 0.07	1.14 ± 0.07	1.15 ± 0.08	1.13 ± 0.06	1.13 ± 0.08	1.15 ± 0.09
Heart rate recovery (1 min)	19.6 ± 6.8	22.5 ± 7.6§	25.5 ± 8.6	20.3 ± 9.4	25.4 ± 8.4§	24.6 ± 7.7
Resting heart rate (beat/min)	68.6 ± 8.4	66.4 ± 8.7§	-	68.8 ± 9.5	63.9 ± 8.8‖	-
Work economy						
Vo_{2peak} (mL · kg^{-1} · min^{-1})	16.0 ± 2.7	13.9 ± 2.1*	-	16.3 ± 3.1	13.8 ± 2.6*	-
Heart rate (beat/min)	106 ± 16.8	93 ± 13.8*	-	102 ± 16.6	86 ± 14.4*	-
Body weight (kg)	84.3 ± 16.4	84.5 ± 16.2	85.0 ± 17.3	85.8 ± 11.8	85.0 ± 11.3	86.0 ± 12.4
Quality of life						
Emotional domain	5.7 ± 0.7	6.2 ± 0.5*	6.1 ± 0.6	5.5 ± 1.1	6.0 ± 0.7*	5.9 ± 0.7
Physical domain	5.3 ± 0.7	6.2 ± 0.4*	6.2 ± 0.7	5.4 ± 1.0	6.0 ± 0.6*	6.1 ± 0.6
Social domain	5.6 ± 0.6	6.5 ± 0.4*	6.5 ± 0.6	5.4 ± 1.3	6.3 ± 0.7*	6.3 ± 0.6
Blood markers						
HDL (mmol/L)	1.31 ± 0.3	1.42 ± 0.4	1.37 ± 0.3	1.29 ± 0.3	1.31 ± 0.3	1.37 ± 0.3
LDL (mmol/L)	2.54 ± 1.0	2.08 ± 1.1	2.43 ± 0.8	2.53 ± 1.1	2.52 ± 1.3	2.54 ± 0.9
Triglycerides (mmol/L)	1.46 ± 0.6	1.37 ± 0.7	1.27 ± 0.4	1.61 ± 0.7	1.56 ± 0.6	1.41 ± 0.6
Ferritin (μg/L)	140 ± 100	100 ± 75*	88 ± 58	138 ± 89	99 ± 73*	104 ± 66
Adiponectin (μg/mL)	5.77 ± 1.9	5.62 ± 1.6	6.39 ± 1.96‡	5.12 ± 1.93	4.83 ± 1.84	5.64 ± 2.26¶
Glucose (mmol/L)	6.0 ± 1.1	5.8 ± 0.9	5.5 ± 0.6	6.6 ± 2.3	6.2 ± 1.2	6.2 ± 1.4
Hemoglobin (g/dL)	13.5 ± 1.0	13.7 ± 1.0	14.3 ± 1.0¶	13.7 ± 1.2	13.9 ± 1.1§	14.2 ± 1.8

Patients who changed their β-blocker dose during the study were excluded from analyses on heart rate. Patients in the analyses were n = 23 to 28 in AIT and n = 23 to 31 MCT. Resting heart rate and work economy were not measured at 6m. Footnotes indicate significant changes. Values are mean ± SD. *RER*, Respiratory exchange ratio; *HDL*, high-density lipoprotein; *LDL*, low-density lipoprotein.
* From BL to 4w ($P < .001$) within groups.
† From 4w to 6m ($P < .05$) between groups.
‡ From 4w to 6m ($P < .05$) within groups.
§ From BL to 4w ($P < .05$) within groups.
‖ From BL to 4w ($P < .01$) within groups.
¶ From 4w to 6m ($P < .01$) within groups.

and relocation (n = 1). At baseline there was no significant difference in Vo_{2peak} between those who turned up and those who did not (26.8 mL·kg^{-1}·min^{-1} [SD 4.9] vs 26.0 mL·kg^{-1}·min^{-1} [SD 4.9] 2-sample *t* test, $P = .62$). Neither was there any significant difference in quality of life.

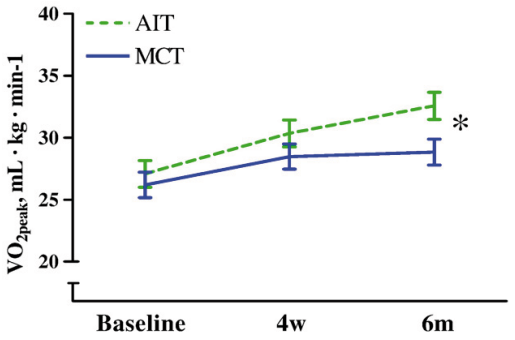
Implementation of interventions

The AIT group attended 16.4 (range 14-19) exercise sessions on the treadmill, and the MCT group, 16.7 (range 14-19). In addition, each subject carried out 16.5 (range 12-19) other training sessions during the 4 weeks. The AIT group exercised at 92% (SD 4.6) of HR maximum during the intervals and reported their subjective exhaustion to be at 6.1 (SD 0.9) at the Borg scale. The MCT group exercised at 74% (SD 3.5) of HR maximum, with a Borg scale of 2.9 (SD 0.9). In the other training sessions at the center, the patients exercised with high intensity in 31% and moderate intensity in 69% of the registered sessions, respectively.

Outcomes

Both groups showed a significant increase in Vo_{2peak} between baseline and 4w. Between 4w and 6m, only the AIT group increased Vo_{2peak} significantly, yielding a group difference at 6m of 3.0 mL·kg^{-1}·min^{-1} ($P = .04$, 95% CI 0.2-5.7 mL·kg^{-1}·min^{-1}) (Table II, Figure 2). Women had a Vo_{2peak} about 5.0 mL·kg^{-1}·min^{-1} less than

Figure 2



Vo_{2peak} in AIT and MCT at baseline, 4w, and 6m. The bars represent ± SEM. *$P < .05$, group comparison.

Table III. Echocardiography variables at baseline (BL) and 4w

	AIT		MCT	
	BL (n = 19)	4w (n = 19)	BL (n = 19)	4w (n = 19)
Systolic function				
S' (cm/s)	7.4 ± 1.4	6.8 ± 1.3	6.9 ± 1.0	6.9 ± 0.9
MAE (mm)	11.5 ± 2.1	11.1 ± 2.3	11.4 ± 1.8	11.7 ± 2.0
Diastolic function				
E (cm/s)	67.7 ± 16	60.2 ± 16*	65.8 ± 15	66.7 ± 15
A (cm/s)	56.2 ± 8	55.6 ± 11	57.1 ± 13	58.5 ± 13
e' (cm/s)	9.4 ± 1.4	9.2 ± 2.0	9.1 ± 0.8	9.1 ± 1.2
a' (cm/s)	10.6 ± 1.7	10.5 ± 1.4	9.4 ± 1.6	9.5 ± 1.7
E/e'	7.3 ± 2.0	6.7 ± 2.0	7.4 ± 1.7	7.6 ± 2.0
E/A	1.2 ± 0.4	1.1 ± 0.4	1.2 ± 0.3	1.2 ± 0.5
DT (ms)	171 ± 38	173 ± 49	182 ± 49	182 ± 50
Volumes				
EF %	48 ± 10	48 ± 9	44 ± 8	46 ± 9
EDV (mL)	103 ± 29	103 ± 32	118 ± 28	111 ± 30
ESV (mL)	54 ± 20	52 ± 18	66 ± 22	61 ± 23

Values are mean ± SD. *S'*, systolic mitral annular velocity; *MAE*, mitral annular excursion; *E*, peak early diastolic mitral flow velocity; *A*, late diastolic mitral flow velocity; *e'*, early diastolic mitral velocity; *a'*, late diastolic mitral velocity; *DT*, deceleration time of the early diastolic mitral velocity; *EF*, ejection fraction; *EDV*, end diastolic volume; *ESV*, end systolic volume.
* Different from MCT ($P = .023$).

that in men, and Vo_{2peak} decreased by 0.2 $mL \cdot kg^{-1} \cdot min^{-1}$ per year of age.

Maximum HR was 143 (SD 17) and did not differ significantly between groups or time of testing. Both groups showed significant improvements in HR recovery between baseline and 4w, with no significant changes between 4w and 6m (Table II).

At baseline, 31 of 38 patients (AIT 13, MCT 14) were classified with reduced diastolic function (impaired 10, pseudonormal 14, and restrictive: 7). The average left ventricular volumes were normal, and EF slightly reduced. No changes were seen in EF, end-diastolic volume, or in any of the mitral annular velocity variables. Early diastolic filling velocity (*E*) decreased after exercise in the AIT group only ($P = 0.023$) (Table III).

Serum adiponectin, ferritin and hemoglobin changed significantly over time (Table II). All 3 domains of MacNew improved significantly between baseline and 4w, and remained so at 6m, with no significant difference between the groups (Table II).

Exercise at home. Most of the subjects were doing exercise training between 4w and 6m; the AIT subjects did more interval training with high intensity (Table IV).

Discussion

Our main finding was that both AIT and MCT training groups showed a significant increase in Vo_{2peak}, HR recovery, and quality of life after a 4-week intense rehabilitation program (at 4w). At follow-up 6 months from discharge (6m), the AIT group showed a further increase in Vo_{2peak}, whereas MCT did not.

Based on previous studies,[4-6,14] we had hypothesized that AIT would increase Vo_{2peak} more than MCT. After 4 weeks of exercise training, there was slight evidence for a greater increase in Vo_{2peak} in the AIT group (group × 4w interaction, $P = .19$). One reasonable explanation for the lack of difference could be the relatively short duration of the training period. The participation in additional training sessions with various intensities at the rehabilitation center may also have reduced the difference between the effects of the 2 training groups.

Low HR recovery is an independent predictor of mortality in patients with cardiovascular disease.[15] In our study, AIT and MCT gave similar, significant increases in HR recovery at 4w. Similar effects of exercise training have previously been reported,[16] whereas others[17] found a higher HR recovery only after 2 minutes. We are not aware of any previous studies comparing the effect of different exercise intensities on HR recovery in CABG patients.

Follow-up after 6 months

The AIT group increased their Vo_{2peak} significantly by home exercise, whereas the MCT group maintained their capacity. We speculate that the greater improvement in the AIT group at 6m is due to more intense exercise training at home, as outlined in Table IV. Others have found reduced exercise capacity after home exercise,[18] but patients attending a similar 4-week rehabilitation program as in ours maintained aerobic capacity at 2 years of follow-up.[19] It might be that such intense programs provide an educational setting and also a "kick-start" for changing the activity patterns for these patients, beyond what is obtained through outpatient rehabilitation.

In a prospective study of men and women with coronary heart disease, Keteyian et al[3] found an approximate 15% reduced risk of death with every 1 $mL \cdot kg^{-1} \cdot min^{-1}$ increase in Vo_{2peak}; hence, the difference seen in our study between AIT and MCT at 6m could be important regarding mortality.

Echocardiography

After 4 weeks of exercise, we found no major changes within or between groups for the systolic function of the left ventricle. Because of the wide range of diastolic (dys) function in the study population, we consider *e'* a more robust marker of the left ventricular diastolic function than *E*, which has a nonlinear relation to diastolic dysfunction because of its load dependency. Hence, the change in *E* must be interpreted with caution. The fact that none of the other variables characterizing diastolic function changed after exercise supports the conclusion that diastolic function was also unaffected by exercise. There are 2 possible explanations for these results. First, the training period might have been too short for

Table IV. Reported exercise training between discharge from the of rehabilitation center (4w) and 6m

Group	Incomplete registration	No exercise training	<3 times per week, moderate intensity	>3 times per week, moderate intensity	>3 times per week, moderate and high intensity
AIT (n = 23)	0	3	3	5	12
MCT (n = 25)	1	2	5	16	1

detectable adaptations to occur,[6,20] and the increase in Vo_{2peak} was thus due to peripheral adaptations. Second, the patients were examined at rest, whereas changes could have been present during activity. There are few similar studies in CABG patients, but previous results in patients with coronary heart disease are in agreement with ours regarding systolic function.[21] Regarding diastolic function, previous studies have found some signs of improvement in both mitral filling and tissue Doppler–derived variables.[21,22] In patients with overt heart failure, however, AIT improves both systolic and diastolic functions significantly.[6]

Blood markers

Serum adiponectin has been reported to increase after moderate-to-high intensity exercise training in subjects with the metabolic syndrome,[5] type 2 diabetes mellitus,[23,24] and obesity,[25] although the data are not consistent.[26] To our knowledge, this study is the first to investigate adiponectin in patients with coronary artery disease undergoing an exercise program. The insignificant changes in adiponectin at 4w may be due to the short training period. Also, it can be caused by the need for a supercompensation period after a training program to reveal the real adaptation. In line with these assumptions, we observed that both groups had increased levels of adiponectin at 6m. Two uncontrolled trials on similar short training periods have found different results.[23,24] Blüher et al[23] found significant increases in subjects with both normal and impaired glucose tolerance, as well as in subjects with type 2 diabetes mellitus after 4 weeks of exercise training. In contrast, Oberbach et al[24] found only significant increase in subjects with impaired glucose tolerance or type 2 diabetes mellitus and not in subjects with normal glucose tolerance.[24] Eriksson et al[27] however found a large increase in adiponectin in healthy men after a 14-day long skiing expedition.

Ferritin decreased significantly in both groups at 4w. In advance, we had no specific hypothesis about changes in ferritin throughout the study, but some studies have linked increased ferritin levels to increased incidence of coronary artery disease (for a review, see, eg, reference 28).

Quality of life

Besides improved physical capacity, the ultimate goal is to improve quality of life for these patients. Quality of life increased significantly in both groups at 4w and remained improved at 6m. Dixon et al[29] maintain that a change of 0.5 in MacNew score is clinically important and equivalent to the improvement seen after revascularization. We saw changes larger than this in all 3 domains from baseline to 4w and therefore argue that both groups had significantly better quality of life after the rehabilitation period. Even more important, this improvement was maintained at the follow-up test.

Conclusions

Vo_{2peak} and HR recovery increased significantly after a brief but intense exercise program of both moderate continuous exercise training (MCT) and AIT in coronary artery bypass patients. Aerobic interval training was superior to MCT in increasing Vo_{2peak} and HR recovery 6 months after ending the formal program. Quality of life increased significantly after 4 weeks of rehabilitation and remained improved for 6 months in both training groups.

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Paper III

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