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Physical Exercise in Clinically Healthy Men and in Patients with Angiographically Documented Coronary Artery Disease with Special Reference to Cardiac Autonomic Control and Warm-up Phenomenon

Doctoral dissertation

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The Research Foundation of Health, Exercise and Nutrition
Kuopio Research Institute of Exercise Medicine
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ABSTRACT

Physical inactivity, poor cardiorespiratory fitness, impaired heart rate variability (HRV) and heart rate turbulence (HRT) are independent predictors of cardiovascular morbidity and mortality both at the population level and among patients with coronary artery disease (CAD). Exercise training is considered beneficial with regard to autonomic nervous system function, although long term randomized intervention trials are still lacking in middle-aged men. Many CAD patients are capable of recruiting endogenous protective mechanisms against repeated bouts of ischemia and demonstrating warm-up phenomenon. Its clinical features and especially its relationships with autonomic control are poorly characterized.

In the cross-sectional setting, the relationships between habitual physical activity and health related fitness and between carotid atherosclerosis and cardiorespiratory fitness were investigated. Also changes in heart rate variability and heart rate turbulence during a six-year period of programmed training in middle-aged men (The DNASCO Study) and the relationships between warm-up phenomenon, HRV and HRT in patients with angiographically documented CAD were studied.

In men with chronic cardiopulmonary or musculoskeletal diseases, total energy expenditure correlated directly with maximal oxygen uptake (VO2max) and inversely with body adiposity, triglycerides and fibrinogen. Furthermore, VO2max correlated inversely with carotid bifurcation intima-media thickness, a surrogate measure of atherosclerosis. During the six-year exercise intervention aerobic threshold increased significantly in the exercise group, while no significant differences were found in heart rate variability or turbulence between the groups. However, improved submaximal cardiorespiratory fitness was associated with favourable changes in HRV. In CAD patients, who underwent two successive exercise tests randomly assigned to four groups with different resting periods between the tests (15-120 min) the percentage of patients demonstrating warm-up phenomenon was 85, 31, 31 and 46, respectively. Ischemic threshold and exercise tolerance were significantly higher during the second test in the group with the shortest resting period. Patients with angiographically less severe disease showed better ischemia adaptation. Furthermore, HRV and cardiac autonomic control were better in patients demonstrating warm-up phenomenon than in those not demonstrating the phenomenon. HRV also correlated with the magnitude of the ischemia adaptation.

In conclusion, habitual physical activity associates beneficially to body fatness, cardiorespiratory fitness and traditional CAD risk factors. Cardiorespiratory fitness independently predicts carotid atherosclerosis, and its changes associate directly with the changes in heart rate variability in middle aged men. In CAD patients, warm-up phenomenon is commonly encountered. Protection disappears quite quickly and is related to cardiac autonomic regulation. Further investigations are necessary to reveal, whether a dose-dependent relationship between regular exercise training and preservation or improvement in cardiac autonomic regulation exists in the aging population, and whether endogenous adaptation to ischemia in CAD can be enhanced with regular physical training.

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Medical Subject Headings: physical education and training; physical fitness; exercise test; atherosclerosis; coronary arteriosclerosis; adaptation, physiological; coronary disease/physiopathology; heart rate/physiology; risk factors; middle aged, male

To all my most beloved ones

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Kuopio, July 2005

Petri Tuomainen

ABBREVIATIONS

AMI	= acute myocardial infarction
AP	= angina pectoris
BMI	= body mass index
BRS	= baroreflex sensitivity
CABG	= coronary artery bypass grafting
CAD	= coronary artery disease
CCS	= Canadian Cardiovascular Society
CHF	= chronic heart failure
CVD	= cardiovascular diseases
DNASCO	= DNA polymorphism and carotid atherosclerosis study
ECG	= electrocardiogram
EE	= energy expenditure
HDL	= high-density lipoprotein
HF	= high frequency
HR	= heart rate
HRT	= heart rate turbulence
HRV	= heart rate variability
IMT	= intima-media thickness
IP	= ischemic preconditioning
LDL	= low-density lipoprotein
LF	= low frequency
LVEF	= left ventricular ejection fraction
PCI	= percutaneous coronary intervention
pNN50	= percentage of RRIs differing >50ms from the previous RRI
PTCA	= percutaneous transluminal coronary angioplasty
REE	= energy expenditure at rest
RMSSD	= root mean square of successive difference of normal RRIs
RRI	= RR-interval
SCD	= sudden cardiac death
SDNN	= standard deviation of normal RRIs
SPVC	= supraventricular premature complex
STD	= ST-segment depression
TEE	= total energy expenditure
TO	= turbulence onset
TS	= turbulence slope
ULF	= ultra low frequency
VAT	= ventilatory aerobic threshold
VLF	= very low frequency
VO2max	= maximal oxygen consumption
VPC	= ventricular premature complex
W/H	= waist to hip ratio

LIST OF THE ORIGINAL COMMUNICATIONS

This thesis is based on the following five papers, which are referred to in the text by their Roman numerals I – V:

I Rauramaa R, Tuomainen P, Väisänen S, Rankinen T. Physical activity and health-related fitness in middle-aged men. Medicine and Science in Sports and Exercise, 1995;27:707-712.

II Rauramaa R, Rankinen T, Tuomainen P, Väisänen S, Mercuri M. Inverse relationship between cardiorespiratory fitness and carotid atherosclerosis. Atherosclerosis, 1995;112:213-221.

III Tuomainen P, Peuhkurinen K, Kettunen R, Rauramaa R. Regular physical exercise, heart rate variability and turbulence in a 6-year randomized controlled trial in middle-aged men: The DNASCO Study. Life Sciences, 2005; in press.

IV Tuomainen P, Vanninen E, Halonen P, Peuhkurinen K. Characterization of the warm-up phenomenon in patients with coronary artery disease. American Heart Journal, 2002;144:870-876.

V Tuomainen P, Hartikainen J, Vanninen E, Peuhkurinen K. Warm-up phenomenon and cardiac autonomic control in patients with coronary artery disease. Life Sciences, 2005; 76:2147-2158.

CONTENTS

1. INTRODUCTION

Physical activity is a crucial health determinant of people throughout their lifespan. Based on the extensive epidemiological research since the 1950`s physical inactivity is now considered as a major risk factor for coronary artery disease. Controlled randomized clinical trials have revealed several plausible mechanisms of the health benefits of regular physical exercise. While the focus in most clinical trials has been in the metabolic pathways, much less attention has been directed towards the role of the autonomic nervous system as a mediator of the health benefits of regular physical activity. There is good evidence to show that poor cardiorespiratory fitness is a major risk factor for coronary artery disease. In general, decreased resting heart rate as a consequence of regular exercise training is an old, simple, and valid parameter of cardiorespiratory fitness and together with heart rate variability reflects the changes in the balance of autonomic nervous system. Animal studies have shown that lowering of heart rate either by exercise or surgical intervention is associated with a retardation of coronary atherosclerosis (Kramsch et al. 1981, Beere et al. 1984). Furthermore, regular exercise therapy (i.e. rehabilitation) enhances both symptom-free and maximal exercise tolerance and performs even better than routine invasive therapy in improving the event-free survival of patients with stable CAD (Hambrecht et al. 2004).

The state of the autonomic nervous function and especially its degeneration is an established and independent indicator of worsened outcome not only in patients with coronary artery disease but also at the population level in the elderly. The improvement in autonomic nervous function and/or its preservation against the effects of aging are important targets of promoting survival and can be affected favorably by exercise training. Resistance training also has several positive health effects and has recently been accepted as a suitable form of exercise in the rehabilitation of cardiac patients in addition to the more studied aerobic exercise.

Exercise has also disadvantages. One major issue is the development of myocardial ischemia due to exercise strenuous enough to increase myocardial oxygen demand over the level of oxygen delivery supplied by occluded coronaries. This concerns not only patients with documented coronary artery disease, but also asymptomatic / undiagnosed subjects. The myocardium is able to utilize endogenous mechanisms against reintroduced ischemic attack. The clinical appearance of this is called warm-up phenomenon and in clinical studies it is encounterd in many patients with coronary

artery disease. The adaptation to ischemia is of limited duration, however. Whether delayed protection in humans exists, is a far more hypothetical issue so far.

The present series of studies have examined the health benefits of regular physical exercise from both preventive and clinical cardiology points of view. Accordingly, the aims were to investigate the relationships between habitual physical activity and health related fitness as well as between cardiorespiratory fitness and the degree of carotid artery atherosclerosis in a random sample of middle-aged men both with and without chronic diseases. Based on these cross-sectional analyses, the main aim was to investigate the changes in cardiac autonomic nervous function in middle-aged men in a randomized controlled six-year exercise intervention trial.

Concerning coronary artery disease, one important aim was to characterize more thoroughly the warm-up phenomenon, i.e. to investigate the prevalence, duration and clinical determinants of endogenous ischemia adaptation in invasively examined patients. Since autonomic nervous function has been studied only occasionally in ischemic preconditioning, one aim was to investigate whether any association between cardiac autonomic regulation and adaptation to myocardial ischemia exists.

2. REVIEW OF THE LITERATURE

2.1. Physical exercise and cardiorespiratory fitness

2.1.1. Basic physiological responses to exercise

Dynamic exercise causes vasoregulatory changes in the heart and peripheral vessels. During isotonic or isometric exercise, where the length of the working muscle fibers alters continuously, the changes are very clear. Responses lead to enhanced perfusion of working skeletal muscle and myocardium not accompanied by any simultaneous limitation of cerebral perfusion. Visceral perfusion together with the perfusion of the kidneys also decreases. In the peripheral vasculature, the vessel resistance is lowered both in working muscle tissue and in skin. This occurs because of the further demand to allow the elimination of excessive body heat (LeWinter & Osol 2001, Shephard 1992).

Generally, the acute responses are likely to be dependent on the duration of the exercise bout. The main limiting factor in very brief (0 – 10 s) exercise is the anaerobic power in the form of the active muscles' loss of anaerobic energy reserves such as creatine phosphate and adenosine triphosphate in that order. With somewhat longer exercise (10 – 60 – 120 s), anaerobic capacity plays also a key role due to the increasing concentrations of lactic acid, especially in the active tissues and to a lesser degree in circulating blood where it also represents a marker of anaerobic metabolism (Shephard 1992).

An exercise period of 5 to 10 minutes is mainly limited by maximal oxygen consumption (VO2max), which is easily reached in an intensive bout of exercise of that duration. The cardiorespiratory responses include a clear elevation in cardiac output plus an even more intense increase in respiratory minute volume. When the production and accumulation of lactic acid exceeds its elimination, the minute ventilation increases more steeply compared to the increase in oxygen consumption and at this point the so called anaerobic threshold has been reached. Also an increase in catecholamine levels of blood can be measured (Von Euler 1974, Shephard 1992). In sustained aerobic exercise of 20 to 30 minutes' duration, hormonal changes are seen on a larger scale, with the concentrations of cortisol and growth hormone also being elevated (Shephard & Sidney 1975, Sidney & Shephard 1978). Induced sweating results in the loss of fluid and minerals, which is the main limiting factor in sustained aerobic exercise of one to two

hours' duration (Shephard 1992). Also an increase in the secretion rate of beta-endorphins is evident (Harber & Sutton 1984).

During even longer bouts of exercise (2 – 5 hours), the glycogen stores of the muscles play a key role in exercise limitation, while in extremely long exercise episodes (longer than 5 hours) fat mobilization is considered to be the main limiting factor of performance capacity. All carbohydrate reserves can be totally exhausted already during 100 minutes, if the intensity of exercise is at the level of 75 % of the VO2max (Shephard 1992). It is especially noteworthy that very long and intense exercise can result in a clearly measurable leakage of enzymes like creatine kinase and lactate dehydrogenase from both active skeletal muscle and myocardial tissue. This may cause disturbances in the diagnosis and differentiation of a real myocardial damage due to acute coronary syndrome especially when acute myocardial infarction (AMI) occurs after vigorous exercise (Cummins et al. 1987).

2.1.2. Cardiovascular risks

Regular long-term physical activity prevents from the development of coronary artery disease. Furthermore, physical activity seems to protect against acute myocardial infarction induced by brief and high-intensity physical stress. However, in physically inactive subjects, especially with one or more coronary artery disease (CAD) risk factors, acute dynamic or isometric stress can trigger an AMI and/or fatal ventricular arrhythmia. In addition to ruptured plaque and coronary artery thrombosis also coronary vasoconstriction even in normal coronaries has been hypothesized to be one plausible underlying factor to SCD induced by physical stress. Impaired recovery of HR after exercise stress test predicts mortality independently of the angiographical severity of CAD (Cole et al. 1999, Vivekananthan et al. 2003). HR recovery has also been suggested to be related with cardiovascular autonomic control. Interestingly, a very recent report of HR behaviour in a bicycle stress test in asymptomatic men (n = 5713) documented three markers of increased risk for SCD during a 23-year follow-up: 1) Pre-test resting HR > 75 bpm (rr = 3.92, 95% CI 1.91 - 8.00), 2) Increase in HR during exercise < 89 bpm (rr = 6.18, 95% CI 2.37 – 16.11), and 3) Decrease in HR < 25 bpm during the first minute of recovery (rr = 2.20, 95% CI 1.02 – 4.74) (Jouven et al. 2005).

2.1.3. Physical exercise and CAD risk factors

Regular physical exercise has favourable effects in most of the traditional and also on other documented risk factors for CAD (Anspaugh et al. 1996, Wood et al. 1998, Pollock et al. 2000). Some overall effects are presented in Table 1. A comparison of the effects of aerobic endurance and resistance training in some parameters of health, cardiorespiratory fitness and CAD risk factors is presented in Table 2. In addition to these preventive effects on cardiovascular morbidity, an even more important consideration is that physical inactivity is a strong and independent risk factor for CAD.

Table 1. The general effects of regular physical exercise on the CAD risk factors.

Risk factor	Response
Systolic blood pressure	↓
Diastolic blood pressure	↓
Serum total cholesterol	↓ / ↔
Serum low density lipoprotein cholesterol	↓ / ↔
Serum high density lipoprotein cholesterol	↑
Serum triglycerides	↓
Insulin sensitivity	↑
Obesity	↓
Smoking	↓ / ?

2.1.4. Effects on morbidity and mortality in middle-aged men

In healthy middle-aged men, physical inactivity and poor physical performance capacity are strong predictors of cardiovascular diseases and cardiovascular mortality (Ekelund et al. 1988, Lakka et al. 1994, Blair et al. 1996, Lee et al. 1999). High fitness level and improvement in physical fitness have been shown to associate with a decline also in all-cause mortality (Sandvik et al. 1993, Blair et al. 1995, Erikssen et al. 1998, Laukkanen et al. 2001). In secondary prevention trials with patients who have suffered an acute

myocardial infarction, the documentation of a significant reduction in mortality due to active exercise rehabilitation has remained less impressive. However, pooled data has revealed an approximately 25 % reduction in overall mortality in patients of programmed exercise arms (Shephard 1992). There is some evidence that regular exercise and enhanced cardiorespiratory fitness may be one way to prevent the progression of atherosclerosis evaluated quantitatively as intima-media thickness (IMT) of carotid arteries by high-resolution B-mode ultrasonography. In middle-aged men without statin treatment, programmed exercise training caused a 40 % reduction in IMT over six years compared to controls (Rauramaa et al. 2004). Determination of IMT with this noninvasive method enables quantitative evaluation of the extent and severity of atherosclerosis (Blankenhorn et al. 1993, Blankenhorn & Hodis 1994). Progression of IMT has been considered as a reasonable surrogate for hard cardiovascular endpoints. Large-scale observational studies in subjects without cardiovascular symptoms have been able to document that moderate levels of physical activity have protective effects against both morbidity and mortality of cardiovascular origin (Paffenbarger et al. 1986, 1993, Leon et al. 1987, Morris et al. 1990). Furthermore, physical fitness has been shown to correlate negatively with atherosclerotic cardiovascular mortality during follow-up periods of 8 to 16 years (Ekelund et al. 1988, Blair et al. 1989, Sandvik et al. 1993).

2.1.5. Exercise training and regression of coronary atherosclerosis

In the pathogenesis of CAD, it has been acknowledged that there are three major components involved in myocardial hypoperfusion. The first is epicardial coronary artery obstruction. The second is dysfunction of the microvascular bed and the third aspect concerns hemostasis and microrheology. In patients with stable angina pectoris, regular physical training is believed to affect all these pathogenetic factors of inadequate myocardial perfusion (Gielen et al. 2001).

Regular exercise training with a low fat diet leads to regression of CAD and improvement in myocardial perfusion (Schuler et al. 1992a, b). It may have beneficial, but perhaps also harmful, effects on the function of thrombocytes and other hemostatic factors. As is the case in healthy persons, regular exercise training evidently increases physical performance also in CAD patients. It also improves symptom-limited performance by increasing ischemic threshold (Ehsani et al. 1981). The same is true in

the case of repeated exercise and consecutive myocardial ischemia leading to endogenous adaptation to ischemia, the so called warm-up phenomenon. Repeated exercise relatively shortly after the first exercise episode both increases ischemic threshold and decreases maximal induced ischemia (Stewart et al. 1995, Tomai et al. 1996).

Regression of coronary artery atherosclerosis determined by quantitative coronary angiography was documented in three prospective and randomized trials in the 20th century. When the effects of lifestyle changes including three hours of exercise per week were investigated, a slight regression in the angiographical percentage of coronary artery stenoses was seen in the active group in contrast to the progression of coronary atherosclerosis observed in the control group. The difference between and within groups proceeded to become more prominent during a follow-up of 5 years and this was also associated with a decreased risk of cardiac events (Ornish et al. 1990, 1998). In another study, which investigated the effects of global risk factor management also including regular physical training the progression of arterial luminal narrowing per year was nearly two-fold worse in the control group over the four-year follow up (Haskell et al. 1994). The third of these prospective trials studied the effects of training and low-fat diet on the progression of coronary atherosclerosis with a six-year follow-up. After one year, the mean luminal diameter had stayed at the baseline level in the intervention group, while it had narrowed in the control group and after the whole follow-up period, beneficial effects in the exercise and diet group were still present (Niebauer et al. 1997). However, it should be underlined that these trials used global lifestyle management and isolated effects of exercise training were not investigated.

In the Heidelberg Regression Study, a possible dose-dependent action of exercise was investigated in a retrospective analysis, where a correlation between exercise driven energy expenditure (EE) and the change in minimal stenosis diameter was determined. Attenuation of coronary artery atherosclerosis was documented at the level of the weekly EE 1500 kcal or more. The regression of coronary artery stenoses was documented only if the EE exceeded the level of 2200 kcal per week. This level of weekly EE is acknowledged to need at least five hours of regular physical exercise (Hambrecht et al. 1993). However, from this point of view, the role of regression of atherosclerosis as the most obvious factor for improved myocardial perfusion seems to be highly questionable. On the other hand, it can be hypothesized that the probability of

regular exercise training to improve myocardial perfusion due to stenosis regression increases after several years (Gielen et al. 2001).

2.1.6. Exercise training and collateral formation in CAD

Long-term regular physical exercise promotes the formation of collateral vessels thereby enhancing myocardial blood flow in animal experiments. However, the findings have been controversial (Neill & Oxendine 1979, Scheel et al. 1981, Cohen et al. 1982). A similar controversy has been observed also in human studies. Previously, no changes appeared in the appearance of visible collaterals during one-year exercise intervention combined with low-fat diet in patients with occlusive CAD and preserved left ventricular systolic function (Heidelberg Regression Study), while among post–AMI patients with ischemic cardiomyopathy, a training period of 8 weeks was able to increase visually determined coronary collateralization in the infarction area (Niebauer et al. 1995, Belardinelli et al. 1998). It has been hypothesized that patients with partially or totally stenotic coronary arteries with preserved or impaired systolic pump function respectively, might react differently to collateralization stimuli. Furthermore, the sensitivity of normal angiography in the documentation of the very small collaterals (i.e. intramyocardial vs. epicardial), which may only be recruited during exercise and consecutive ischemia, is probably far too low (Gielen et al. 2001). It was established already some time ago that visualization of the collaterals in coronary angiography is much more dependent on the function of the collateral vessel rather than simply its anatomical existence. More precisely, visualized filling of collateral channels might require as severe as greater than 90 % diameter stenosis before it causes sufficient limitation in the antegrade flow in the culprit coronary artery (Gensini & da Costa 1969). Once pronounced pressure gradient between the prestenotic and poststenotic segments of the coronary vasculature has developed, the consequences are both an increase in flow through small and pre-existing collateral channels and an increase also in their dimensions (Fulton 1963a, b, Burchell 1983). The acute appearance of previously invisible collateral channels has been documented in patients developing coronary artery spasm during angiography (Takeshita et al. 1982, Tada et al. 1983). The filling of the collaterals is thought to occur within 60 to 90 seconds after total coronary artery occlusion and in the case of one vessel disease, this can be visualized by using

contralateral injection of contrast media during balloon inflation during coronary angioplasty (Rentrop et al. 1985).

2.1.7. Endothelial dysfunction of coronary arteries and exercise training

It has been documented in several human studies that there is a relationship between the major risk factors for CAD and endothelial vasodilatory dysfunction (Chowienczyk et al. 1992, Treasure et al. 1992, Nitenberg et al. 1993, Johnstone et al. 1993, Sumida et al. 1998, Gielen et al. 2001).

The synthesis and release of nitric oxide (NO) play a key role in coronary arterial vasomotion. A diminished level of NO in the vessel smooth muscle cell layers leads to endothelial dysfunction. NO synthesis and release are affected by mechanical stimuli and endogenous or pharmacological agonists. The first documentation of the changes at coronary endothelial function in humans was obtained from a study where acetylcholine infused intracoronarily caused paradoxical vasoconstriction of the coronary artery segments with atherosclerosis in subjects with atypical chest pain (Ludmer et al. 1986). The main determinants of the NO concentration have been listed as follows: (a) The availability of the NO precursor molecule L-arginine; (b) The changes in NO synthesis due to conformational changes, expression or genetic polymorphism of the endothelial NO synthase (eNOS) enzyme; (c) The rate of breakdown of NO due to the action of reactive oxidative species (ROS; highly reactive radicals, i.e. •OH and H_2O_2) (Harrison 1997).

The results of the studies examining supplementation with L-arginine have remained controversial, however. In stable CAD patients, the supplementation of the precursor molecule of NO did not improve vascular function, while positive effects were documented in patients with hypercholesterolemia and congestive heart failure (CHF) (Drexler et al. 1991, Creager et al. 1992, Hambrecht et al. 2000a, Blum et al. 2000). The expression of eNOS in endothelial cells is reported to be attenuated during exposure to TNF-α, oxidized LDL and hypoxia in vitro and the downregulation of eNOS has been reported to be significant in atherosclerosis (Harrison et al. 1995, Wilcox et al. 1997). Genetic polymorphism of eNOS has also been reported (Nakayama et al. 1997, Pulkkinen et al. 2000). The relationship between increased levels of highly reactive radicals (or ROS) and endothelial dysfunction linked to atherosclerosis has been documented. Furthermore, an antioxidant, ascorbic acid, was shown to cause reversal of

this endothelial dysfunction in CAD patients after long-term administration (Rajagopalan et al. 1996, Gokce et al. 1999). The most potent endogenous antioxidative enzyme is the extracellular superoxide dismutase (ecSOD) and endogenous NO has been hypothesized to stimulate both the expression and the release of this enzyme from smooth muscle cells of the vessels. The activity of this enzyme has reported to be lowered in CAD patients and its levels have also been associated with the vasodilatory capacity of the radial artery (Landmesser et al. 2000). Interestingly, exercise training has been proposed to have favourable effects on the expression of ecSOD (Fukai et al. 2000, Kojda et al. 2001).

The effects of exercise training on coronary endothelial dysfunction have also been studied prospectively. In an animal model, it was found that 16 weeks of exercise training in pigs improved the vasorelaxation mediated by endothelial NO after coronary occlusion (Griffin et al. 1999). In an earlier human study on the effects of regular intensive physical training for 4 weeks in CAD patients with endothelial dysfunction, the exercise intervention caused a significant increase in the average peak flow velocity measured by intracoronary Doppler wire. In addition to improved coronary flow in the active group, the acetylcholine induced coronary vasoconstriction, as determined by quantitative angiography, was reduced by more than 50 % after 4 weeks of training compared to the baseline (Hambrecht et al. 2000b). From this point of view, regular physical training can be claimed to have favourable effects on the preservation of endothelial vasomotion in patients with CAD. These protective effects may be important in both chronic and acute coronary syndromes. The true prognostic significance of the vasodilatory dysfunction of coronary endothelium does need more investigation, although in a couple of prospective studies a relationship between endothelial dysfunction and patient outcome in CAD has been documented (Suwaidi et al. 2000, Schächinger et al. 2000). It was suggested that the improvement in myocardial perfusion resulting from enhanced coronary endothelial function may be seen even after only a few weeks of regular training (Gielen et al. 2001).

2.1.8. Exercise training and myocardial microcirculation

Small coronary arteries play a crucial role in the regulation of vascular resistance of coronary circulation and have significant effects on the myocardial blood flow and its distribution (Rubio & Berne 1975, Gielen et al. 2001). NO and atrial nariuretic peptides

act via cyclic GMP to evoke coronary vasodilatation. Adenosine is one of the most potent known endogenous coronary vasodilating agents. It has been documented in an animal model that its production increases progressively due to increased myocardial oxygen consumption and demand and that exercise training can enhance the responsiveness and sensitivity of resistance vessels to adenosine (DiCarlo et al. 1989, Kostic et al. 1992).

In animal models exercise training has increased myogenic coronary resistance vessel responsiveness, the overall cross-sectional microvascular area and has enhanced vascular permeability in arterioles (Muller et al. 1994, Huxley et al. 1997, White et al. 1998). In patients with CAD, exercise training seems to increase coronary flow reserve in response to intracoronary administration of adenosine (Hambrecht et al. 2000b).

2.1.9. Microrheology, thrombogeneity and exercise training

The results of the studies on the effects of physical training on microrheology and blood viscosity have remained controversial with respect to different subject groups. Regular exercise training has beneficial effects on blood viscosity in healthy subjects and patients with peripheral vascular disease but not in patients with CAD and related lowered left ventricular function (Ernst 1987, Reinhart et al. 1998).

Physical exercise affects both platelet numbers and function and also blood coagulation. The effects may be opposite, when acute and regular long-term exercise are compared. Acute and intensive physical stress increases both platelet numbers and aggregation, thus favoring thrombus formation (Prisco et al. 1994). In contrast, regular and long-term physical exercise has been shown to have more favorable effects on platelet function. It also seems to increase the content of cGMP in the platelet pool (Wang et al. 1995). In CAD patients recovering from acute myocardial infarction physical training has been documented to cause a decrease in the level of coagulation factors. It must be noted though that this attenuation of blood coagulability also leads to a reactive decrease in anticoagulation factors (Suzuki et al. 1992). Nonetheless, the sum of these effects on coagulation and thrombus formation in CAD patients lies on the favourable side.

2.1.10. Resistance exercise

Muscle mass and strength decreases by about 30% between the ages of 30 –60 years. This is due to both normal aging and also the decrement in the amount of physical exercise. Therefore, additive resistance training of moderate intensity has been recommended for people of all ages in different fitness programs (Larsson et al 1979, American College of Sports Medicine position stand 1990, Pollock & Vincent 1996). Aerobic exercise training has been used and recommended in the rehabilitation of patients with cardiovascular disorders. Accordingly, resistance training can also increase submaximal aerobic fitness in the healthy elderly (Ades et al. 1996). In addition to the increase in aerobic and maximal cardiorespiratory fitness, endurance training has favorable effects also on the well known CAD risk factors such as elevated blood pressure and serum lipid levels (Pollock et al. 2000) (Table 2.). It seems to be the case that physical training modifies autonomic nervous balance in the form of increased HRV, an acknowledged marker of better outcome in CAD patients. These positive effects have been widely documented only with regular aerobic exercise training.

Resistance training has probably been thought to be harmful and even perhaps risky for both primary and secondary prevention in the cardiovascular patient group as a whole. Large scale studies on resistance training are still lacking and only recently have updated recommendations for cardiac patients been published (Bjarnason-Wehrens 2004). Occasionally, an excessive hypertensive reaction may occur during resistance training. This is especially harmful in cardiac conditions with impaired systolic function (McCartney & McKelvie 1996). The risk evaluation and promotion of resistance training should be individually adjusted in different subgroups of patients with cardiovascular problems, however. Some studies have documented that in patients with CAD, but with preserved left ventricular function, adequately supervised and optimally performed resistance training does not increase the risk for adverse events compared to aerobic endurance exercise (Wenger et al. 1995, Shephard & Balady 1999, Polloc et al. 2000). Positive effects of regular resistance training have also been reported in patients with peripheral vascular disease (McGuigan et al. 2001).

Basically, increases in blood pressure depend on load intensity and duration. Maximal BP values are attained when the load intensity is between 75 – 90 % of the maximal voluntary contraction of the working muscle mass and repetitions are made until exhaustion. It is noteworthy that a simultaneous Valsalva maneuver accentuates

this hypertensive reaction (MacDougall et al. 1985, Fleck & Dean 1987, Fleck 1988). Thus it is understandable why resistance training has been an unpopular exercising method for cardiovascular patients, since many potentially fatal complications can occur during and immediately after a strenuous bout of resistance stress. Hypertension can cause arterial rupture and intracranial hemorrhage, whereas the rapid hypotension following strenuous stress may result in syncope. If cardiac output is hazardously limited, malignant arrhythmias can appear with or without underlying ischemia with the diminished coronary flow acting as their trigger. Furthermore, the markedly increased afterload increases myocardial oxygen consumption together with worsening myocardial perfusion. A long-lasting decrement in coronary perfusion can produce a permanent myocardial injury. The Valsalva maneuver causes a decrease in heart rate via an autonomic nervous reflex arc. The resulting extreme bradycardia has been documented to trigger malignant arrhythmias including ventricular fibrillation (Pollock et al. 2000). Hemodynamic alterations during resistance muscle work are considered to be evoked by sensory nerve fibers reacting mainly to metabolic changes in the working muscle tissue (McCloskey & Mitchell 1972, Thimm & Baum 1987, Rybicki et al. 1984, Baum et al. 1995).

As acknowledged, resistance training cannot be recommended and prescribed to all patient groups. New recommendations for cardiac patients based on a thorough risk assessment have been published (Pollock et al. 2000, Giannuzzi et al. 2003). In CAD patients, who have undergone revascularization procedures, there are no major studies which would have examined the safe time schedule for initiation of physical training after PCI. It is still recommended that training should not be started less that 2 – 7 days post PCI. After CABG the main limiting factor is the recovering stability of the sternum. Severe stress to the upper body should be avoided for the first three months of recovery (Bjarnason-Wehrens 2004).

Table 2. The effects of aerobic endurance and resistance training on some parameters of health, cardiorespiratory fitness and CAD risk factors (Adopted from AHA Science Advisory, Pollock et al. 2000)

	AEROBIC	RESISTANCE
Bone mineral density	+ +	+ +
Body composition		
Percentage of fat	- -	-
Lean body mass	0	+ +
Strength	0	+ + +
Basal metabolism	+	+ +
Glucose metabolism		
Insulin response to glucose challenge	- -	- -
Basal insulin levels	-	-
Insulin sensitivity	+ +	+ +
Serum lipid levels		
LDL cholesterol	- / 0	- / 0
HDL cholesterol	+ / 0	+ / 0
Heart rate (at rest)	- -	0
Stroke volume (at rest & maximal)	+ +	0
Blood pressure (at rest)		
SBP	- / 0	0
DBP	- / 0	- / 0
Maximal oxygen uptake	+ + +	+ / 0
Submaximal & maximal endurance time	+ + +	+ +

+ = small, ++ = medium and +++ = large increase; - = small, -- = medium and --- = large decrease; 0 = values remain unchanged.

2.1.11. Proinflammatory cytokines, atherosclerosis and exercise

Atherosclerosis is an inflammatory disease (Ross 1999). High-sensitivity C-reactive protein (CRP) is a useful marker in the detection of low degrees of inflammation and an increase in its levels has been associated with cardiovascular events (Albert & Ridker 1999, Ridker 2001, Blake & Ridker 2001, Koukkunen et al. 2001). Two proinflammatory cytokines, interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), are produced during various stress reactions such as infections, AMI and other types of

tissue damage. IL-6 is considered as the major stimulus for the production of CRP in the liver and they correlate directly with each other (Heinrich et al. 1990, Miyao et al. 1993). However, conflicting opinions about the role of IL-6 have been presented recently. It has been hypothesized that IL-6 derived from skeletal muscles might potentially inhibit the biological effects of TNF-α and a decrease in the TNF-α level due to physical exercise has also been documented. Therefore, one possible pathway in prevention of the progression of atherosclerosis by regular exercise is hypothesized to be attenuated insulin resistance due to decreased TNF-α concentrations (Pedersen et al. 2001, 2004) (Figure 1). Long term exercise is known to have beneficial effects on the atherogenic activity of mononuclear blood cells in persons prone to CAD (Smith et al. 1999). Globally, the antiatherosclerotic mechanisms via the possible anti-inflammatory effects of regular physical exercise have remained unclear, however. Whether the suggested beneficial IL-6 excretion from skeletal muscle tissue and its assumed anti-inflammatory effects can be enhanced with regular physical training including resistance exercise, remains to be further studied.

Necrosis of the myocardial tissue resulting from AMI is related to the release of IL-6 and TNF-α due to activation of mononuclear cells. An increase in the IL-6 level seems to predict AMI in clinically healthy subjects and mortality in CHF patients (Ridker et al. 2000, Frangogiannis et al. 2002, Kell et al. 2002). During acute coronary syndromes the main source of IL-6 seems to be of cardiac origin (Miyao et al. 1993, Neumann et al. 1995, Deliargyris et al. 2000, Frangogiannis et al. 2002). Furthermore, myocardial infarction size and collagen formation have been shown to associate with the IL-6, but not with the TNF-α concentration after AMI (Puhakka et al. 2003). An earlier study on AMI patients showed that the TNF-α level was related to the severity of myocardial injury (Hirschl et al. 1996). Thus, the changes in cytokine levels may reflect more than simply the inflammatory process. In post-AMI patients with a high risk for future events, the TNF-α concentration seems to be constantly elevated as also occurs in CHF patients (Levine et al. 1990, McMurray et al. 1991, Ridker et al. 2000).

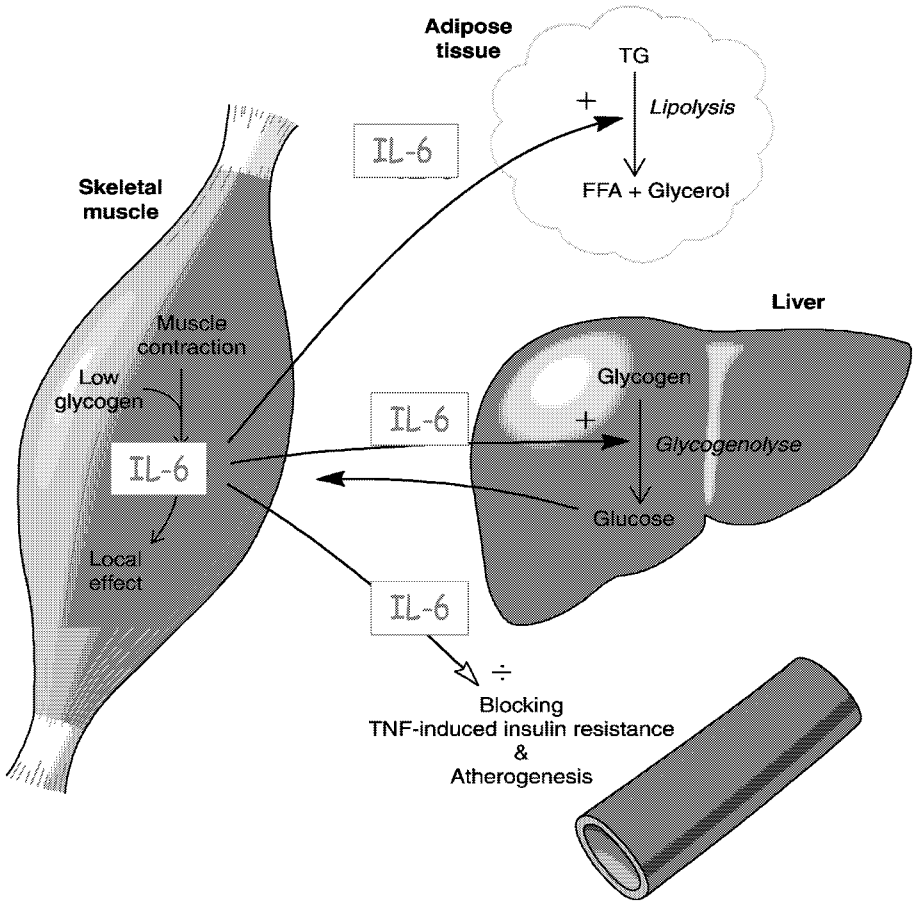


Figure 1. A scheme for the secretion of cytokine IL-6 from a skeletal muscle tissue and its general effects. It has been suggested that IL-6 derived from skeletal muscle has anti-inflammatory effects and it may alleviate TNF-α induced insulin resistance and ultimately atherogenesis.

2.1.12. Regular physical exercise in the primary prevention of CAD

Already three to five decades ago it was shown in large observational studies in Great Britain and the U.S. that the level of physical activity at work or on leisure time correlated inversely with CAD morbidity and mortality and this relationship has been confirmed by later trials. When physical activity is calculated in kilocalories per day and/or week, certain limits for increased risk have been proposed depending on the study population. In subjects doing physically hard work, the risk of CAD increased if energy expenditure was less than 8500 kcal/week, while in a student population the risk increased if energy expenditure in habitual physical activity was less than 2000 kcal/week (Morris et al. 1953, 1966, Paffenbarger & Hale 1975, Paffenbarger et al. 1970, 1978, 1986, 1995, Leon et al. 1987, Miller & Paffenbarger 1992). On the contrary to the assessment of physical activity, cardiorespiratory fitness can be reliably determined using a variety of parameters in exercise stress testing with (or without) respiratory gas analyses. In a previous study, leisure time physical activity correlated positively with increased treadmill test performance, which further correlated negatively with the risk for CAD (Leon et al. 1987). In exclusively middle-aged male populations, cardiorespiratory fitness was associated with a marked reduction in CAD mortality. A high fitness level was typically related with lower HR and BP at rest, higher maximal HR and BP, lower levels of serum lipids and lower frequency of smoking (Lie et al. 1985, Ekelund et al. 1988). This supports the hypothesis that physical activity is associated with a favourable CAD risk factor profile. However, it should be noted that also genetic factors can cause selection bias in observational studies on the effects of exercise training on the outcome of chronic diseases (Kujala et al. 2002).

2.1.13. Exercise rehabilitation in cardiovascular disorders

Several randomized controlled clinical trials and pooled data from systematic reviews have confirmed positive effects of exercise training on physical performance and quality of life and point to a positive effect on both cardiovascular and all-cause mortality in patients with cardiovascular disorders (Kujala 2004). The main results in patients with CAD and CHF are presented in Table 3.

Table 3. A summary of meta-analyses on the effects of exercise rehabilitation therapy in CAD and CHF.

Authors	*Patients*	*N*	*Outcome*
Jolliffe et al. (2001)	CAD	7683	All-cause mortality ↓
			Cardiac mortality ↓
			Non-fatal AMI ↔
Taylor et al. (2004)	CAD	8940	All-cause mortality ↓
			Cardiac mortality ↓
			Non-fatal AMI & revascularization ↔
Smart & Marwick (2004)	CHF	2387	All-cause mortality ↔
			Combined events (mortality & AE) ↔
Piepoli et al. (2004)	CHF	801	All-cause mortality ↓

↑ and ↓ = statistically significant change compared to controls; ↔ = no significant change; CAD = coronary artery disease; CHF = congestive heart failure; AMI = acute myocardial infarction; AE = adverse event.

2.2. Cardiac autonomic regulation

2.2.1. Basic anatomy and physiology of cardiovascular autonomic nervous system

The autonomic nervous regulation of the cardiovascular system is divided into two different and functionally opposite counterparts called the sympathetic and parasympathetic nervous systems. They differ not only in their anatomy but also at neurotransmitter and receptor level (Bannister & Mathias 1999). The autonomic nervous innervation of the heart is constructed basically as follows. The afferent sympathetic nerves originate from the stellate ganglia and from the caudal halves of the cervical sympathetic trunks, while the afferent parasympathetic, i.e. vagal, nerves originate from the vagus nerve and the recurrent laryngeal nerves. Both divisions connect to each other and form the ventral and dorsal cardiopulmonary plexuses (Janes et al. 1986). The afferent signals to the central nervous system arise from both chemoreceptors and mechanoreceptors located in the baroreceptor centers in the carotid sinuses, aortic arch and the heart (Mathias & Bannister 1999, LeWinter & Osol 2001). The centers of spinal cord, medulla, hypothalamus and cortex via their influences on hypothalamus integrate these afferent inputs in the central nervous system (Willis 1993) (Figure 2).

The efferent nerves consist of pre- and postganglionic neurons. In the sympathetic system, the preganglionic neurons originate from the spinal cord's thoracolumbal region and the postganglionic neurons further from pre- and paravertebral ganglia, the postganglionic nerves having longer fibers. In the parasympathetic system, the preganglionic neurons originate from the nucleus ambiguus of the lateral medulla. In contrast to the sympathetic system, vagal ganglions are localized very close to the organs and thus the postganglionic neurons possess rather short axons (Willis 1993).

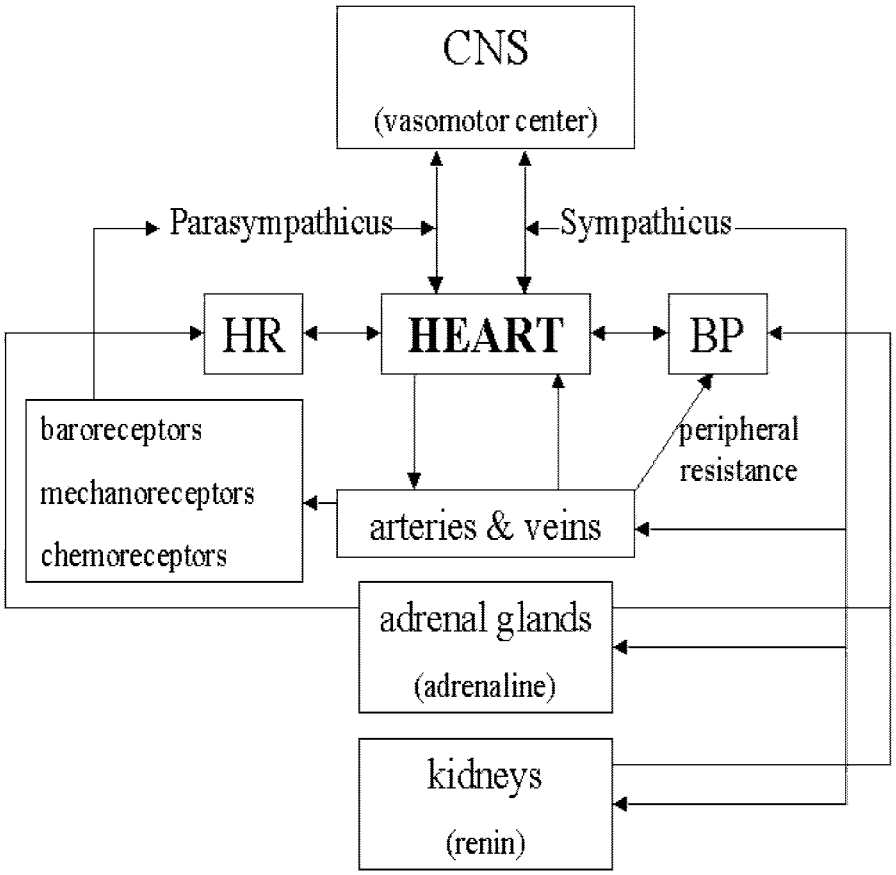


Figure 2. A simplified scheme for the basic connections of cardiovascular autonomic nervous regulation. CNS = central nervous system, HR = heart rate, BP = blood pressure.

The neurotransmitter in all preganglionic synapses as well as in postganglionic parasympathetic synapses is acetylcholine, while in most postganglionic sympathetic synapses, the neurotransmitter is noradrenaline (Willis 1993). There is a difference also in the speed of action and responses between the two divisions. The responses in the end organs can be seen in a few seconds after sympathetic nervous stimulation, while in the case of parasympathetic nervous activation the end organ's responses require only few milliseconds. The so called autonomic nervous tone consists of the highly sensitive balance between both the sympathetic and parasympathetic arms of the autonomic nervous system. They both function in a continuous and interactive manner. The sympathetic nervous activation leads to increased atrioventricular conduction velocity in the AV-node and also to increased heart rate with the influences of its parasympathetic counterpart being directly opposite (Willis 1993). From the anatomical aspect the innervation of the sinus node originates mainly from the right sympathetic and parasympathetic (vagus nerve) nerves and the innervation of the AV-node originates mainly from the nerve branches of the left side (Zipes 1990, 1991).

In addition to the autonomic efferent nerve-ends, also the afferent nerves differ in their localization in the myocardium. Generally, parasympathetic afferent nerves have an intramural location in the endocardium while the sympathetic afferent nerves have an epicardial localization The sympathetic nerves dominate in the anterior wall of the left ventricle and stimulation of autonomic nerve-ends caused by anterior ischemia (i.e. basically perfusion area of LAD) results in sympathetic responses (Webb et al. 1972, Barber et al. 1984). These reflexes cause an increase in heart rate and blood pressure, unless the contractility of the left ventricle has been markedly impaired, and naturally the further increased rate-pressure-product (RPP) represents also an increase in myocardial oxygen consumption. Both of these components are excellent drug targets e.g. blockade of the beta-adrenergic receptors of sympathetic nervous system with beta-blockers. The parasympathetic nerves dominate in the posterior and inferior wall of the left ventricle and autonomic nervous stimulation by inferoposterior ischemia leads to parasympathetic responses in hemodynamics. These reflexes cause a decrease in both heart rate and blood pressure and the action of this reflex arc is also named the Bezold-Jarisch reflex (Webb et al. 1972, Barber et al. 1985, Robertson et al. 1985).

The peripheral vessels in cardiovascular system receive direct sympathetic innervation. These autonomic synapses are mainly responsible for the peripheral vascular resistance. While sympathetic nervous activation in heart causes an increase in

heart rate and force of myocardial contraction resulting in elevated cardiac output (minute volume), in peripheral sites of action it results in vasoconstriction and this leads to increased peripheral vascular resistance and increased blood return to the right atrium the latter also enhancing cardiac output (Willis 1993, LeWinter & Osol 2001) (Figure 2.).

2.2.2. Heart rate variability (HRV)

2.2.2.1. History of heart rate variability

Short-term variability of heart rate and blood pressure was first reported by Hales already in the 18th century (Hales 1733, Lewis 1994). Interestingly, the first clinical studies concerned the fields of obstetrics and neonatology (Hon 1958, 1996, Hon & Yeh 1969, Välimäki et al. 1970, Välimäki & Tarlo 1971, Tarlo et al. 1971), but the first study of sinus arrhythmia, later recognized as a very simple and basic marker of HRV, and its correlation to mortality in coronary artery disease was also reported already in 1965 (Schneider & Costiloe 1965). Later, cornerstone studies evaluating the prognostic significance of decreased heart rate variability in patients with coronary artery disease and after acute myocardial infarction were reported. (Kleiger et al. 1987, Rich et al. 1988, Malik & Camm 1990, Farrel et al. 1991, Bigger et al. 1992). The development of computerized analysis methods in the late twentieth century has greatly promoted the usefulness and utilization of this noninvasive, indirect, measure for evaluation of the cardiac autonomic regulation.

2.2.2.2. Physiological background of HRV

The function of the sinus node is modulated by efferent impulses from the sympathetic and parasympathetic nervous systems. Both the sinus node and atrioventricular node are highly affected by changes in the autonomic nervous function. Sympathetic stimuli leads to noradrenaline release, accelerating the slow diastolic depolarization and this evokes an increase not only in heart rate, but also in atrioventricular conduction velocity. Parasympathetic stimuli release acetylcholine from the vagus nerve initiating the slow diastolic depolarization causing opposite responses in heart rate and atrioventricular conduction. At rest, the vagal system is the main controller of heart rate

(Willis 1993, Bannister & Mathias 1999). Since measurement of the variability of p-wave to p-wave intervals from the electrocardiogram is somewhat more difficult, determination of RR-interval variability has been accepted as a reasonable surrogate for detecting dynamic changes in the sinus node function.

Respiration causes changes in heart rate and this phenomenon is more commonly known as respiratory sinus arrhythmia. Afferent pulmonary input causes changes in the central nervous system control of efferent parasympathetic activity, which is inhibited during inspiration. In frequency domain analysis of heart rate variability respiratory sinus arrhythmia is detected in the high frequency area (0.15 – 0.4 Hz) and it has been proposed to reflect vagal modulation of heart rate, but the evidence has remained controversial (Davidson et al. 1976, Eckberg 1983, Kollai & Mizsei 1990, Malliani et al. 1991, Hayano et al. 1991, Ori et al. 1992). Increased tidal volume associates with increased heart rate variability in the high frequency component. The same is seen in the case of decreased breathing frequency, when the increase in heart rate variability is in addition shifted towards the low frequency component (0.04 – 0.15 Hz) (Eckberg et al. 1983, Saul et al. 1989, 1991, Brown et al. 1993, Taha et al. 1995).

In contrast to vagal stimuli, the effects of sympathetic impulses are believed to be detected in the low frequency area (Malliani et al. 1991, Pagani et al. 1997). Also these findings have remained controversial, and the effects of parasympathetic output have proposed to appear also in the low frequency area (Saul et al. 1990, Koh et al. 1994, Hopf et al. 1995, Kingwell et al. 1994, Eckberg et al. 1997). Also position seems to play a role in heart rate variability and the low frequency component has been suggested to represent both sympathetic and parasympathetic activity in the upright position, while mainly vagal activity is involved in supine position (Pomeranz et al. 1985, Pagani et al. 1986). Furthermore, the effects of sympathetic and parasympathetic impulses on heart rate may not always be opposite. The baroreflex loop is also another important mechanism involved in the modulation of both heart rate and blood pressure variability. The responses caused by the baroreceptor-β-sympathetic reflex are usually detected in the low frequency area (Madwed et al 1989).

Compared to the low and high frequency components, the physiological background of the very low (0.003 – 0.04 Hz) and ultra low (≤ 0.003 Hz) frequency components of heart rate variability is still somewhat obscure. These components represent over 90 % of the total heart rate variability determined from Holter recordings lasting 24 hours. In registrations of five minutes` duration, the power spectrum of the very low frequency

component is still measurable, but determination of the ultra low frequency power needs clearly longer periods of RR-interval data (Akselrod et al. 1981, Hayano et al. 1991, Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology 1996). The renin-angiotensin system and thermoregulation have been suggested to be involved in very low frequency heart rate variability and also the vasomotor tone and/or baroreflex loop may play a role in the variability (Hyndman et al. 1971, Sayers 1973, Kitney 1975, Akselrod et al. 1981, 1985, Lindqvist et al. 1989). Furthermore, the very low frequency component seems to be influenced by parasympathetic components. While respiratory sinus arrhythmia, which mainly represents vagal control, can be eliminated with vagal blockade due to atropine or vagotomy (Akselrod et al. 1985, Pomeranz et al. 1985), these interventions cause almost total abolition of heart rate variability in all (i.e. high, low and very low) frequency components (Akselrod et al. 1981, Hayano et al. 1991). Thus, spontaneous beat-to-beat variation in heart rate is of multifactorial origin, and all underlying mechanisms have not been completely resolved.

Heart rate variability is impaired in many disease states (see below), but the clinical significance of abnormal values of heart rate variability measures in healthy persons is unknown. In apparently healthy middle-aged subjects, decreased heart rate variability was documented in 1 to 12 % of the persons using the criteria of the standard deviation of normal RR-intervals (SDNN) < 70 or ≤ 105 ms, respectively. However, no cardiovascular deaths or marked arrhythmic events occurred during an average follow-up period of 2.5 years (Grimm et al. 2003a).

2.2.2.3. Editing methods of the RR-interval data for the determination of HRV

In the raw ECG data, various ectopic or non-sinus beats and pure artifacts in the ECG signal form the major sources of error and bias concerning the calculation process of HRV. Several methods have been developed to edit the RR-interval data to increase the reliability of interpretation of physiological signals. A few methods have been commonly approved and the necessity of editing has been pointed out to be crucial. Though, the usage of different editing methods may depend on the parameters analyzed and also on the length of the ECG registration. There is no single "gold standard" method for all analyzed parameters and for recordings of different duration. In both time and frequency domain measures, a deletion method has previously been documented to

be equal or better editing method in the case of short-term registrations (Lippman et al. 1994). A more recent report indicated that in frequency domain analysis, interpolation performs better leading to smaller errors in the editing process of especially long-term (24 h) but also short-term (5 min) registrations (Salo et al. 2001).

2.2.2.4. Effects of gender and aging on HRV

Aging has been shown to reduce HRV both in ambulatory 24-hour ECG registrations and in short-term supine measurements. The reduction is affected by gender and in an aging male population, the attenuation of HRV seems to be more global (Huikuri et al. 1996, Stein et al. 1997, Fukusaki et al 2000). In the Framingham Heart Study, decreased HRV predicted total mortality in the elderly (Tsuji et al. 1994). In that particular study less than a half of the subjects were male, however. Referring to a recent study, HRV was reported to be reduced by up to 20 % during a 5-year follow-up period in healthy sedentary subjects (Agelink et al. 2001).

2.2.2.5. Effects of exercise training on HRV and association with fitness

The results from the studies investigating the effects of regular aerobic exercise and enhanced cardiorespiratory fitness on HRV have been controversial. Endurance-trained subjects seem to have higher HRV and higher parasympathetic activity compared to sedentary controls. The results are comparable also in older men (Goldsmith et al. 1992, De Meersman 1993, Yataco et al. 1997), but opposite findings have also been reported (Reiling & Seals 1988). Regular physical training has been found to decrease resting heart rate and increase HRV and vagal tone in healthy and sedentary subjects (Seals & Chase 1989, Stein et al. 1999, Schuit et al. 1999, Tulppo et al. 2003, Hautala et al. 2004). There are also studies, where resting HR has been shown to be decreased without any major changes in HRV. On the other hand, among trained subjects, increased HRV seems to be associated with the improvement in maximal oxygen consumption or exercise performance (Boutcher & Stein 1995, Loimaala et al. 2000, Hautala et al. 2004). Recent results in a group of middle aged men showed that during a one-year training period, HRV increased in the exercise group and decreased in the control group. Alterations were seen only in total and very low frequency power of spectral

analysis of HRV when only short-term ECG-registrations at supine rest were used in the determination (Uusitalo et al 2002).

2.2.2.6. HRV in CAD and after AMI

Reduced HRV associates with increased mortality after acute myocardial infarction (Wolf et al. 1978, Kleiger et al. 1987, Farrell et al. 1991, Bigger et al. 1992). A decrease in HRV has been documented also in patients with stable and uncomplicated coronary artery disease (Airaksinen et al. 1987, Hayano et al. 1990, Wennerblom et al. 2000). Decreased HRV has been related to a higher incidence of cardiac events even at the population level (Algra et al. 1993, Tsuji et al. 1996). Reduced HRV may also be correlated with the angiographic degree of CAD, but the evidence has remained controversial (Airaksinen et al. 1987, Rich et al. 1988, Hayano et al. 1990). In one early study, where the mortality risk in post-MI patients was assessed with time domain HRV analysis, the risk of death was over five times higher in patients with SDNN < 50 ms compared to the patients in the other dichotomy (Kleiger at al. 1987). Also frequency domain parameters of HRV have been shown to predict mortality after MI (Bigger et al. 1992).

Changes in HRV occur in CAD and especially after AMI. However, improvement of myocardial blood supply with either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) has not been shown to increase HRV in some studies (Niemelä et al. 1990, 1992). Furthermore, decreased HRV correlates with many cardiovascular risk-factors including systolic blood pressure decreased left ventricular systolic function, serum insulin and serum triglyceride levels and the duration of smoking (Kupari et al. 1993, vanBoven et al. 1998, Gerritsen et al. 2000, Jokinen et al. 2003). Treatment of CAD with β-blockers and ACE-inhibitors has favorable effects on heart rate variability. Both drug types enhance vagal control and total heart rate variability (Flapan et al. 1992, Binkley et al. 1993, Molgaard et al. 1993, Niemelä et al. 1994, Sandrone et al. 1994, Bonaduce et al. 1994).

2.2.2.7. Effects of exercise training on HRV in CAD and in CHF

Results from the clinical studies on the influences of cardiac rehabilitation with exercise training on HRV in CAD patients after AMI have been controversial (Mazzuero et al.

1992, Malfatto et al. 1996, Leitch et al. 1997). In a non-randomized study in patients recovering from major CAD events, a cardiac rehabilitation program with exercise training increased RRI and RRI-variability, VO2max and BRS compared to controls. Furthermore, improved VO2max correlated with HRV (Lucini et al. 2002). In a randomized study in post-AMI and post-CABG patients 3-month period of programmed physical training six times per week increased both exercise capacity and HRV compared to the group with programmed training only two times per week. The difference remained also after a one-year follow-up (Tygesen et al. 2001).

The findings in patients with left ventricular dysfunction have also been conflicting. In CHF, physical training has been shown to increase HRV and cardiac parasympathetic tone (Adamopoulos et al. 1995). Improvements among the trained patients have been seen throughout the whole 24 hours and also only during the day. Unfavourable changes in the untrained patients, on the other hand, have been suggested to be present during both waking and sleeping hours (Kiilavuori et al 1995). However, in patients with heart failure after acute myocardial infarction, HRV was not prominently enhanced during eight weeks of high-intensity physical training (Duru et al 2000).

2.2.3. Heart rate turbulence (HRT)

2.2.3.1. Determination of HRT

Heart rate turbulence (HRT) is a newly introduced method investigating short-term fluctuations in heart rate after single ventricular extrasystoles primarily due to responses in cardiovascular autonomic nervous regulation to changes in blood pressure. It expresses a phenomenon termed ventriculophasic sinus arrhythmia representing a physiological chronotropic response of sinus rhythm after single ventricular premature complexes. This response is biphasic consisting of an early acceleration and then a later deceleration of sinus rhythm after a single ventricular extrasystole, and it is expressed by two different numerical parameters; turbulence onset (TO) and slope (TS) (see below). Heart rate turbulence has been primarily described using spontaneous ventricular ectopic activity in ambulatory electrocardiogram recordings (Schmidt et al. 1996), and secondarily this phenomenon has been constructed "artificially" in an electrophysiological test model using stimulated (paced) premature complexes.

The formula for calculation of turbulence onset:

$$TO = \frac{(RR_1 + RR_2) - (RR_{-2} + RR_{-1})}{(RR_{-2} + RR_{-1})} \times 100\ \%$$

In this equation the RR-intervals RR_{-2} and RR_{-1} represent the second and the first sinus beats preceding the ectopic ventricular beat and correspondingly RR_1 and RR_2 represent the first and the second sinus beats after the ectopic beat. In contrast to the equation of TO, turbulence slope (TS) is defined as the regression line, which is assessed over any sequence of five subsequent RR-intervals within the first 20 sinus beats following the premature index beat, with the maximum positive slope and it is expressed in ms/RRI (Schmidt et al. 1996, 1999, Guzik & Schmidt 2002) (Figure 3).

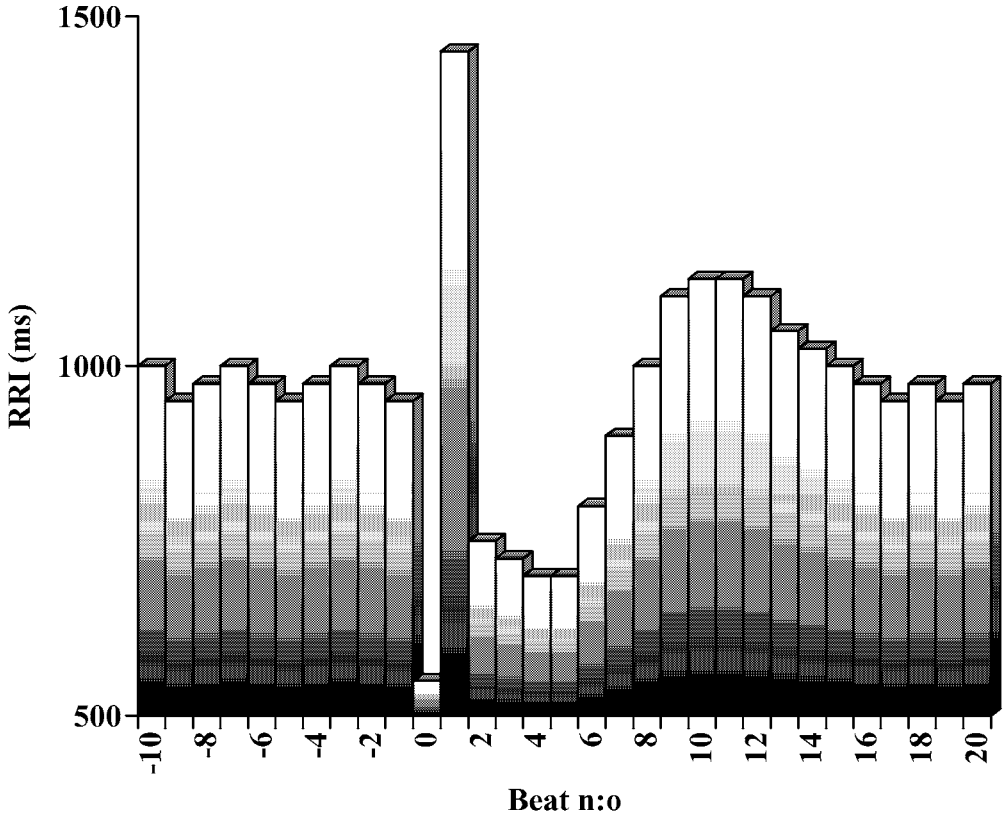


Figure 3. A scheme for the behavior of RR-intervals in the heart rate turbulence phenomenon. The shortest RRI (i.e. beat number 0) represents the coupling interval preceding the ventricular ectopic beat and the longest RRI (i.e. beat number 1) represents the compensatory pause following the ectopic beat. The early acceleration of HR (i.e. shortening of RRI:s) is seen within the beats number 2-5 and the late deceleration of HR (i.e. lengthening of RRI:s) is seen between the beats 5 – 10. HR has normally stabilized within 15 –20 beats following the ectopic complex.

2.2.3.2. Physiological background of HRT

The observed fluctuation in heart rate after single ventricular ectopic beats is thought to be due to arterial blood pressure variations and there is a negative correlation between systolic blood pressure and sinus rate after a ventricular extrasystole. It has been hypothesized that the decrease in blood pressure during the compensatory pause initiates a stimulus in the baroreflex loop leading to diminished parasympathetic activity and causing a brief phase of tachycardia. Turbulence onset measures the magnitude of this early phase, which is passed within two to four beats in normal conditions (Schmidt et al. 1999, Schneider et al. 1999, Malik et al. 1999, Davies et al. 2001). More slowly the heart rate decelerates first under the level of previous mean heart rate before returning to baseline level. It is hypothesized that an increase in blood pressure due to increased sympathetic outflow ultimately leads to decreased heart rate due to recovering vagal activity. This late phase has normally reached its completion within 20 beats, with the longest RR-interval (i.e. the lowest heart rate) appearing at the point of the $8 - 10^{th}$ sinus beat (Figure 3). The magnitude of this late response is measured by the turbulence slope (Schmidt et al. 1999, Schneider et al. 1999, Malik et al. 1999, Marine et al. 2002). It has been reported that heart rate turbulence correlates with heart rate variability and baroreflex sensitivity (Schmidt et al. 1996, 1999, Ghuran et al. 2002, Lindgren et al. 2003). In healthy middle-aged subjects, turbulence slope, which seems to be more closely correlated with baroreflex sensitivity, at least in coronary artery disease, is not so prone to false positive values than turbulence onset when the dichotomizing cut-off points of previously reported prognostic trials are used (5 and 19 %, respectively) (Schmidt et al. 1999, Ghuran et al. 2002, Barthel et al. 2003, Grimm et al. 2003b).

The documentation of the comparability of spontaneous heart rate turbulence and the model of induced phenomenon during electrophysiological testing is quite limited. In a small patient group both the turbulence onset and slope after spontaneous and induced ventricular ectopic beats were found to be similar and no significant differences in blood pressure reactions and estimated baroreflex sensitivity were documented between these two models. Thus, the authors considered the model of electrophysiologically induced ventricular extrasystoles as a valid method assessing heart rate turbulence under controlled conditions (Roach et al. 2003).

There are diverging results concerning the influence of the prematurity of the ventricular extrasystole, i.e. the coupling interval, on heart rate turbulence. In a recent

study, the prematurity seemed to be related to turbulence onset, but not to turbulence slope (Schwab et al. 2004). Earlier the prematurity of the coupling interval was shown to correlate positively with turbulence onset and negatively with turbulence slope in subjects with normal left ventricular ejection fraction. A somewhat weaker relationship between the complex prematurity and turbulence onset only was observed in patients with lowered ejection fraction, reflecting attenuated baroreflex responsiveness in this patient group (Savelieva et al. 2003).

The site of origin, or more likely the pacing site, may not have as significant an effect on heart rate turbulence as the coupling interval. When extrasystoles are induced from two basic pacing sites in the right ventricular apex (RVAP) and right ventricular outflow tract (RVOT), turbulence slope does not correlate with the site of pacing, but the values from both sites correlate relatively strongly with each other the behavior of turbulence onset remaining more unclear. In that study the negative correlation between turbulence onset and the coupling interval (see above) was observed only in the case of apical generating site, however. With respect to the lack of influence of the point of origin on heart rate turbulence, the authors concluded the computation based on spontaneous extrasystoles in ambulatory Holter electrocardiogram to be a reliable method assessing heart rate turbulence (Schwab et al. 2004).

The underlying mechanisms of normal heart rate turbulence have mainly remained unresolved, but influences of the autonomic nervous system have been hypothesized to be primary effectors. In patients undergoing electrophysiological testing, both turbulence onset and slope reverted to abnormal values after vagal blockade due to administration of atropine. Linked together with the finding that atrial-atrial (AA) intervals are predominant in the changes in RR-intervals, the results suggest that normal heart rate turbulence is strongly based on the preservation of parasympathetic influence on the sinus node (Marine et al. 2002).

2.2.3.3. HRT after atrial premature complexes and changes in atrioventricular nodal function

A quite similar chronotropic response of sinus rhythm is observed also after single supraventricular premature complexes, but the magnitude of this oscillatory phenomenon seems to be blunted. In subjects without structural heart disease, turbulence onset was found to be more positive, turbulence slope was attenuated and the

increase in heart rate was delayed by one beat after spontaneous atrial extrasystoles compared to ventricular ectopy. The same was true also when premature beats were induced in electrophysiologic testing in a small subgroup of these same subjects (Lindgren et al. 2003). In a previous study, the findings concerning turbulence onset and slope were similar with the onset being clearly positive after induced atrial extrasystoles. Therefore, no significant correlation existed between turbulence onset after atrial and ventricular premature complexes in contrast to turbulence slope (Savelieva et al. 2003).

The effects of the coupling interval and the pacing site on heart rate turbulence have also been studied with atrial extrasystoles during electrophysiologic testing. In patients with and without normal left ventricular ejection fraction neither turbulence onset nor slope was influenced by the atrial premature beat coupling interval in either of the groups (Savelieva et al. 2003). Turbulence onset, but not slope, after atrial premature complexes has been reported to have a significant correlation with the coupling interval, when the response is induced from the lateral part of the coronary sinus, but not from the high right atrium stimulating site (Schwab et al. 2004).

Autonomic perturbations due to heart rate turbulence after ventricular ectopy may not be limited only to the effects on heart rate and RR-intervals, since reactions also in atrioventricular conduction velocity have been observed. However, the findings have been conflicting. In a very recent electrophysiological study, atrioventricular conduction was documented to respond 25 to 15 times weaker in the early and late phase of heart rate turbulence compared to the response of RR-intervals, while earlier nearly all of the fluctuations in RR-intervals were reported to be explained by the corresponding fluctuation in atrial-atrial (AA) intervals (Wichterle et al. 2003, Marine et al. 2002). Therefore, this issue needs more investigation.

2.2.3.4. Assessing methods of HRT

As mentioned earlier, heart rate turbulence can be determined from Holter ECG or from ECG registered in the electrophysiologic laboratory; the first method investigating spontaneous and the second induced ventricular ectopy. Reliable calculation of both turbulence onset and slope requires an RR-interval segment consisting of altogether 20 beats without artifacts or any other ectopic complexes than the index extrasystole. More thoroughly, 5 preceding and 15 following RR-intervals around the premature ectopic

complex, including the coupling interval and compensatory pause, should be of pure sinus origin. The index extrasystole also must express a certain degree of prematurity and a postextrasystolic pause to produce a typical heart rate turbulence pattern. Therefore single ventricular ectopic complexes with the coupling interval of ≤ 80 % and the compensatory pause of ≥ 110 % of the mean duration of the five preceding pure sinus RR-intervals are normally included in the signal averaged calculation of heart rate turbulence parameters (Schmidt et al. 1996, 1999, Schneider et al. 1999, Malik et al. 1999, Guzik & Schmidt 2002).

2.2.3.5. HRT in cardiovascular diseases and in risk stratification

The method of assessing heart rate turbulence was first developed and tested in a two year follow-up study in 100 coronary artery disease patients, of whom the majority had a positive history of myocardial infarction. All possible cut-off points both of heart rate turbulence onset and slope were statistically tested to maximize the predictive power for mortality. Both parameters were then dichotomized to normal and abnormal range normal values being ≤ 0 % and ≥ 2.5 ms/RR-interval for turbulence onset and slope, respectively (Schmidt et al. 1996). After this pilot study, the method and the established dichotomization were validated retrospectively in patients surviving acute myocardial infarction using the data from MPIP (Multicentre Postinfarction Program) and EMIAT (European Myocardial Infarction Amiodarone Trial) studies. At present the same dichotomization has been used in all retrospective and prospective risk stratification studies.

HRT has been found to be an independent predictor of total mortality and both fatal and non-fatal cardiac arrest after AMI (Schmidt et al. 1999, Ghuran et al. 2002, Barthel et al. 2003). In patients with the first AMI treated with primary PCI TS increases and TO decreases after reperfusion is achieved, whereas HRT remains attenuated in patients with unsuccessful adequate reperfusion. This indicates a better preservation of baroreflex responsiveness with rapid reperfusion and may indicate more severe microvascular dysfunction in patients with suboptimal PCI outcome (Bonnemeier et al. 2003).

2.3. Warm-up phenomenon

2.3.1. History and definition

Already in the 18th century William Heberden (1785) described a patient, whose exercise induced angina pectoris disappeared during intensively continued stress, and called it a walk-through phenomenon. In the 20th century, Wayne and Graybiel investigated the effects of eating, outside temperature and repetitive exercise on effort angina and described an obvious variant to this previous phenomenon, "angina sine dolor", which since has been linked to the warm-up phenomenon. Over three decades later MacAlpin and Kattus (1965) published a more thorough report applying adaptation to exercise in angina pectoris. It is defined as an attenuation of signs of myocardial ischemia during repeated physical exercise and in later years it has been demonstrated in numerous studies.

2.3.2. Links to other endogenous protective mechanisms

Ischemic preconditioning (IP) is an endogenous protective mechanism against repeated periods of myocardial ischemia. The phenomenon was first discovered by Murry et al. (1986), who found that the size of myocardial infarction caused by coronary occlusion could be limited by short periods of preliminary ischemia in the healthy dog heart. Later it has been noticed that ischemia and reperfusion cause many changes in the preconditioned myocardium. These changes include a decrease in the amounts of adenine nucleotides, increased level of creatine phosphate, decreased level of glycogen, increased level of intracellular free glucose, increased level of sarcoplasmic phosphorus, and increased levels of cellular K+ and water. The cornerstone response in tissue metabolism is a decrease in the energy demand during reintroduced ischemia (Jennings 1997).

In human left ventricular muscle in vitro, adenosine A1 receptor stimulation results in improvement in post-ischemic function and in vivo aminophylline, an A1 receptor antagonist, prevents IP during PCI. IP can also be produced by administering phenylephrine which causes α-1-adrenergic receptor stimulation (Banerjee et al. 1993, Cleveland et al. 1996, Claeys et al. 1996). Opioid receptor stimulation has been shown to reduce the size of AMI and this might be linked to ATP-sensitive K+ channels. It has

also been suggested that β-adrenergic, muscarinic and bradykinin receptors may play a role in triggering of IP (Yao & Gross 1993, Wall et al. 1994, Brew et al. 1995, Schultz et al. 1996, 2001).

Activation of protein kinase C (PKC) from its inactive cytosolic form to its active membrane form occurs after adenosine binds to its membrane receptor. This is proposed to play a key role in the IP in rabbits and rats, although some discrepancy of the results has been noted in different species (Liu et al. 1991, Cave et al. 1993, Ytrehus et al. 1994, Mitchell et al. 1995, Vahlhaus et al. 1996, Kitakaze et al. 1996). Activated PKC phosphorylates adenosine triphosphate (ATP) sensitive potassium channels resulting in the opening of these channels and a reduction in the duration of action potential (de Jong & de Jonge 1997). Adenosine seems to be an important mediator both in the acute phase of the phenomenon and also in the delayed phase of protection after 24 hours, which is also described as the second window effect (Baxter et al. 1994, de Jong et al. 2000). The immediate response in IP is assumed to result from the activation of membrane receptors, whereas the delayed response is thought to concern the overexpression of heat shock proteins (Ovize et al. 1994a). The role of adenosine and PKC as primary initiators of the pathway has remained controversial, however. In many in vitro animal studies with isolated cardiomyocytes exposed to short preliminary period of lack of oxygen followed by a prolonged period of anoxia and subsequent reoxygenation the degree of IP has remained quite low (Armstrong et al. 1995, Cave et al. 1996, Gottlieb et al. 1996, Liu et al. 1996). The role of IP in ischemia-reperfusion injury has been simulated in vitro. A pharmacological simulation of IP with a PKC activator shortly before the onset of a prolonged ischemic episode can cause clear preventive effects in isolated rat cardiomyocytes. This is reflected as attenuation of Ca^{2+} -ion overload in the ischemic cardiomyocytes resulting in a very intense protection against a lethal injury during reoxygenation (Ladilov et al. 1998). Based on this, it has been suggested that IP is a genuine phenomenon of cardiomyocytes rather than a more global phenomenon at the tissue level involving different cells within the myocardium (Piper & Ladilov 1997).

There are differences between species also in the minimal duration of primary ischemia needed to activate the protective phenomenon as well as in the influences of repeated induction ischemia periods. The minimal duration of effective primary ischemia may vary from 2.5 to 5 minutes. Furthermore, the effects of multiple ischemic periods on the developing myocardial infarct size and further postischemic left

ventricular dysfunction seem to differ between species. The initial protection achieved may even be lost during constantly repeated ischemic attacks (Li et al. 1990, Cohen et al. 1994, Iliodromitis et al. 1997, Kremastinos 1997). Also the findings of the influences of the degree of the luminal coronary occlusion and the degree of reperfusion between the inductive and sustained ischemic period on the IP have remained somewhat controversial (Ovize et al. 1992, Schultz et al. 1995, Koning et al. 1995, Kapadia et al. 1997). Interestingly, when the primary stimulus is not efficient enough to promote significant myocardial ischemia (e.g. rapid ventricular pacing or stretching of myocardium) or when ischemia is even targeted to another organ, a limitation in the myocardial infarct size can still be observed (Ovize et al. 1994b, Koning et al. 1996, Gho et al. 1996).

In addition to animal models, IP has been demonstrated in human myocardium. In vitro, the role of PKC in IP was first confirmed using human myocardium (Speechly-Dick et al. 1995, Ikonomidis et al. 1997). ATP-sensitive potassium channels are believed to be the end-effector of IP, since the blockade of these channels with glibenclamide abolishes the cardioprotection provided by both adenosine and the PKC activator. In addition to ATP sensitive potassium channel blockade, administration of the α1-adrenergic antagonist seems to prevent the IP, while an agonist activating the same receptor causes only partial cardioprotective effects during ischemia in human atrial trabeculae tissue (Cleveland et al. 1997). In humans, this IP phenomenon has been demonstrated in percutaneous coronary interventions during repeated coronary angioplasty (Deutsch et al. 1990, Airaksinen & Huikuri 1997) and it has also been induced during both atrial and ventricular pacing (Williams et al. 1985, Ylitalo et al. 2000). In addition to these interventional studies, preinfarction angina pectoris has been shown to provide considerable protection of the myocardium and correlate with lower risk of complications and better outcome during the acute phase of myocardial infarction (Muller at al. 1990, Anzai et al. 1994 Ottani et al. 1995, Andreotti et al. 1995, 1996, 1999, Kloner et al. 1998a, b, Noda et al. 1999).

In cardiac surgery, a better preservation of ATP stores due to IP during coronary artery bypass grafting (CABG) has been reported in a study, where myocardium was preconditioned by short episodes of preliminary cross-clamps of the aorta and the operative procedure was performed during intermittent but longer periods of cross-clamping and ventricular fibrillation (Yellon et al. 1993, Alkhulaifi et al. 1994). However, an opposite finding has also been reported (Jenkins et al. 1995). This

conservation of cellular energy stores has been accepted as a key common pathway in this phenomenon during a prolonged ischemic period (Vuorinen et al. 1995). Myocardial preconditioning may have also harmful effects during CABG. It has been shown to cause a greater outflow of cardiac enzymes and even result in non-Q-wave injuries instead of triggering protective effects during CABG involving retrograde or antegrade cardioplegia (Perrault et al. 1996, Kaukoranta et al. 1997). It would be logical to assume that IP should act synergistically with traditional cardioplegia during cardiopulmonary bypass. Especially in cases, where cardioplegia cannot be optimally performed, the role of IP becomes more pronounced (Galinanes et al. 1995). On the other hand, cardiopulmonary bypass itself may act as a stimulus for IP via its adenosine and catecholamine releasing effects and it can be abolished by their receptor blockade (Burns et al. 1995). Thus, the models investigating the recruitment of IP differ quite markedly between PCI and CABG procedures. Concentrating on a regional myocardial ischemia and only one target vessel, these models resemble each other most, when CABG is performed in a minimally invasive fashion in the beating heart (i.e. off-pump) (Subramanian et al. 1995, Perrault & Menasche 1997, Penttilä et al. 1999, 2001). In an animal model, functional recovery of the myocardium was enhanced with administration of adenosine during reperfusion after a 3-hour period of cardioplegia. Since ATP concentrations were similar in the adenosine and control groups, the improvement in myocardial function was suggested to relate mainly to the observed increase in coronary flow (Ledingham et al. 1990). During angioplasty in humans, adenosine has been reported to be even more effective than classical preconditioning with repeated vessel occlusions in triggering of IP and its administration seems to be well tolerated (Leesar et al. 1997). Iatrogenic opening of ATP-sensitive potassium channels has been suggested as a promising method also during cardioplegic arrest (Menasche et al. 1995, 1996). In addition to adenosine, also an inhibitor of Na+/H+ ion exchange seems to enhance myocardial recovery after prolonged ischemia. This ion exchanger is acknowledged to play a marked role in lethal ischemia-reperfusion injury at the cellular level (Klein et al. 1995, Koike et al. 1996). An adequate exploitation of pharmacologically induced IP and its clinical advantages have been a target of interest for at least one decade, but there are still many unsolved questions in this field of cardioprotection.

It has also been documented that there is a relationship between IP and diminishing of arrhythmogeneity and this may well be independent of the ischemia limiting effect

itself. Patients experiencing preinfarction angina within 24 hours before AMI have been shown to exhibit a decreased tendency to experience malignant ventricular arrhythmias (Tamura et al. 1997). During coronary angioplasty, ventricular ectopy has been shown to decrease during repeated vessel occlusion despite there being similar objective and subjective signs of ischemia (Airaksinen & Huikuri 1997). The same antiarrhythmic effect has been proved in ambulatory monitoring. In patients with consecutive ischemic episodes in Holter registrations, ventricular ectopy and arrhythmias during the recurrent ischemia period appeared to be less frequent during the latter period. The overall reduction in the number of ectopic beats and ventricular tachycardias required the interval length between ischemic episodes to be of 30 minutes maximum (Pasceri et al. 1996). This time-scale shares a similarity with the observation from a study on the duration of warm-up phenomenon (Stewart et al. 1995). In this particular Holter study and the above mentioned PCI study, the maximal ST-segment change was not different between repeated ischemic episodes. Furthermore, in the Holter study, the heart rate at the time of the maximal ST-segment elevation was lower during the episodes with less arrhythmias. These findings suggest that this antiarrhythmic effect might be independent of the anti-ischemic effect itself and that vagal influences might be involved (Pasceri et al. 1996, Airaksinen & Huikuri 1997).

2.3.3. Characterization and potential mechanisms in humans

Warm-up phenomenon is thought to be a clinical variant of ischemic preconditioning, but the evidence has remained somewhat unclear. Adenosine has been found to be an important mediating vasoactive substance in ischemic preconditioning. The phenomenon itself is considered to be mediated through ATP sensitive potassium channels (Ylitalo et al. 1996, Tomai et al. 1999a) and it can be prevented with the antidiabetic drug, glibenclamide, which reversibly blocks these channels (Tomai et al. 1999b). Unlike in ischemic preconditioning there is controversy about the roles of adenosine and ATP-sensitive K-channels in warm-up phenomenon (Bogaty et al. 1998, 2001, Tomai et al. 1997, 1999b). Furthermore, other aspects like downregulation of myocardial contractility or increased myocardial blood flow provided by collateral channels after the primary exercise induced ischemic episode do not appear to offer a satisfactory explanation for warm-up phenomenon (Bogaty et al. 1998, 2001).

Although the warm-up phenomenon is commonly encountered in patients with coronary artery disease, the exact prevalence and duration of the phenomenon and its clinical determinants have been poorly characterized. In patients with stable angina, warm-up phenomenon is commonly observed 10 – 15 minutes after first exercise, whereafter increased ischemia tolerance has been suggested to wane relatively quickly. The warm-up phenomenon has been documented to disappear partially within 10 minutes to two hours in humans (Tomai et al. 1996). The results of another study suggested that warm-up protection disappeared within 30 minutes (Stewart et al. 1995).

Coronary vasodilatation and enhanced oxygen supply have been hypothesized to be the primary mechanisms involved in warm-up phenomenon (Jaffe & Quinn 1980, Tomai et al. 1996, Ylitalo et al. 1996, 2001). Warm-up phenomenon can be prevented by administering the vasodilator nisoldipine, which selectively blocks Ca2+ channels (Ylitalo et al. 2001). Furthermore, the warm-up phenomenon has been suggested to be related to the angiographical severity of the coronary artery disease. Ylitalo et al. (1996) found a negative correlation between the degree of the left anterior descending coronary artery stenoses and enhanced ischemia tolerance, while other previous studies have shown an inverse relationship between stenosis severity and vasodilatory capacity of the affected coronary arteries (Uren et al. 1994, DiCarli et al. 1995). It has also been suggested that decreased regional myocardial oxygen consumption or peripheral mechanisms might be involved in the warm-up phenomenon (Okazaki et al. 1993, Stewart et al. 1995, Tomai et al. 1996, Ylitalo et al. 1996). On the contrary, increased cardiac oxygen consumption is known to be correlated to the degree of coronary vasodilatation (Knabb et al. 1983, Raatikainen et al. 1991). Therefore, coronary circulation and probably regional changes in myocardial metabolism play important roles in the endogenous protection against myocardial ischemia.

Although ischemia adaptation is believed to disappear primarily within one to two hours, there are findings for a re-emergence of this phenomenon after a couple of days (Ylitalo et al. 1996, 2001). This reappearance of endogenous adaptation is called second-window protection. It has been hypothesized that peripheral mechanisms might be involved in the protection observed after a resting period of two hours (Tomai et al. 1996). However, no definitive evidence for second window protection induced by exercise has yet been reported in patients with coronary artery disease. As previously demonstrated in animal models, the delayed protection seems to appear within 24 hours

after the primary ischemic episode and finally to disappear within 96 hours (Baxter & Yellon 1997).

In warm-up phenomenon, the role of the initial stimulus, in other words the amount of ischemia per se during the primary phase has been discussed but its importance has remained unclear. It has been hypothesized that the appearance of warm-up protection might be dose-dependent. Bogaty et al. (2003) performed a study, where the effects of different levels of ischemia in the first test on warm-up phenomenon were investigated. The results showed that significant ischemia in the first exercise was essential if one wished to induce attenuation of the ischemic signs in the second and a symptom limited exercise test. If the ischemic load was kept below the normal ischemic threshold, adaptation to ischemia was not inducible. However, also the mildest ischemia and exercise could still enhance exercise capacity in the second test. In contrast to these findings, the results of a previous study of Kay et al. (2000), who investigated the same question but by utilizing a slightly different protocol, showed that first submaximal ST-segment depression was attenuated in the second test also during the mildest exercise protocol in patients demonstrating warm-up phenomenon.

2.4. Summary of the review of the literature

Physical inactivity and poor cardiorespiratory fitness have been emphasized as major and independent risk factors for coronary artery disease. Degeneration of cardiac autonomic nervous function is also an independent and strong indicator of worsened outcome in patients with CAD, this being evident also at the population level. The key advantages of regular aerobic exercise are both the increment in cardiorespiratory fitness and favorable influences on autonomic nervous balance. The studies on the influences of exercise interventions on autonomic nervous balance have given controversial results and long term randomized intervention trials in middle-aged men are still lacking. Regular physical exercise training has beneficial effects on the progression of coronary atherosclerosis and on coronary flow and myocardial perfusion. Also resistance training has cardiovascular health benefits and is recommended as a part of the rehabilitation of CAD patients. Physical exercise has also disadvantages, e.g. development of myocardial ischemia in CAD patients. However, in CAD, the myocardium is able to recruit endogenous protection against repeated ischemia and its clinical expression, warm-up phenomenon, can be seen in many CAD patients. Warm-up phenomenon is thought to be related to the severity of CAD. Its duration and underlying factors have not yet been adequately studied and cardiac autonomic nervous function has not been studied in warm-up phenomenon.

3. PURPOSE OF THE PRESENT STUDY

The main purpose of this thesis was to study cardiovascular and cardiorespiratory effects of physical exercise in an aging male population and in coronary artery disease.

The more precise aims were:

1. to investigate the relationships between habitual physical activity and health related fitness in a random sample of middle-aged clinically healthy men and in men with chronic diseases.
2. to investigate the relationship between cardiorespiratory fitness and the degree of carotid artery atherosclerosis in middle-aged men.
3. to investigate the changes in heart rate variability and turbulence in middle-aged men in a randomized controlled six-year exercise intervention trial.
4. to investigate the prevalence, duration and clinical determinants of warm-up phenomenon in patients with angiographically verified CAD.
5. to investigate the relationship between cardiac autonomic regulation and ischemia adaptation in warm-up phenomenon.

4. SUBJECTS

4.1. Eastern Finnish middle-aged men (Studies I - III)

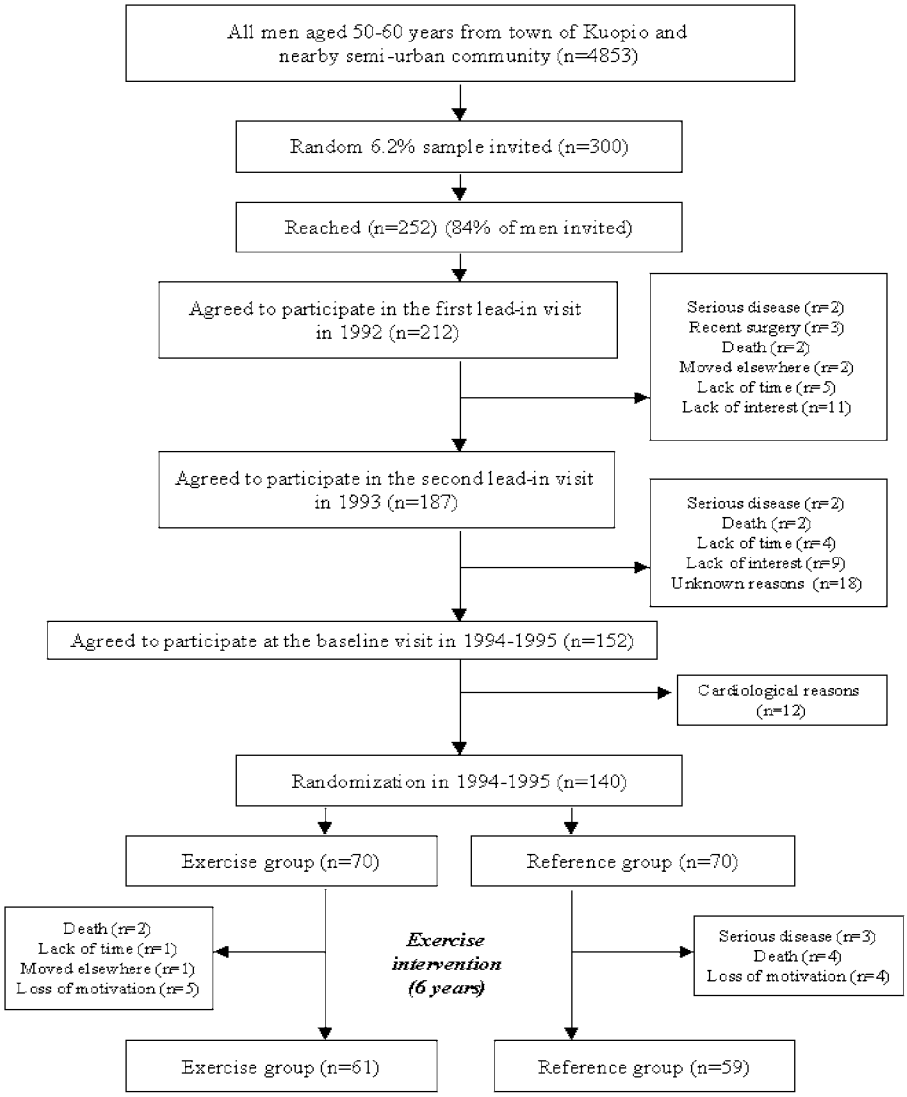


Figure 4. The flow-chart of the middle-aged male subjects (Studies I – III) (Adopted from Rauramaa et al. 2002).

This population consisted of a 6.2 % random sample of Eastern Finnish men aged 50 to 60 years at the beginning of the first study of this thesis (n = 4853). The majority of the subjects lived in the city of Kuopio (82%) and the rest lived in a nearby semiurban community (18%). Of the 300 invited men, there were 212 who were willing to participate (Study I) (Figure 4). In the group of those unwilling to participate, 41% had reported cardiorespiratory, musculosceletal or metabolic symptoms or diseases and the rest did not report any chronic diseases or regular medication. Of the participants, 82 had a positive history of some cardiovascular disease. The most common cardiovascular diagnosis was hypertension (29%). Coronary artery disease had been diagnosed in 26 % (n = 43) of the subjects. Of these, 14 subjects had a positive history of myocardial infarction, 17 had effort angina and the rest were categorized as having other ischemic heart disease. The most common non-common cardiovascular diagnoses were osteoarthritis (7%) and bronchial asthma (5%). The 163 subjects having complete exercise stress test and carotid ultrasound data made up the study population of Study II. After one year, the subjects were invited to a follow-up examination of Study I and 187 (88 %) participated (Figure 4).

The same study cohort continued to form the study population of the DNASCO study (DNA polymorphisms and carotid atherosclerosis). The total number of subjects was 140, who were randomly assigned to the exercise (n = 70) or the control group (n = 70). Exclusion criteria were diseases or physical conditions restricting regular exercise training, malignant diseases and mental states restricting cooperation. During the six-year intervention altogether 20 subjects (9 in the exercise group and 11 the control group) dropped out. Among these lost cases there were 6 deaths (2 in the exercise and 4 in the control group) and 4 severe diseases (all in the control group) (Figure 4). HRV was determined among 100 subjects with qualified ambulatory ECG recordings (baseline – six years) and HRT was determined among those with single VPCs (n=73). Altogether 91/100 subjects had undergone maximal ergometer tests with respiratory gas analyses at baseline and after the intervention (Figure 5). The baseline characteristics of the patients are presented in Table 4 and the cardiovascular medication of the subjects on the study on HRV and HRT (III) is presented in Table 5.

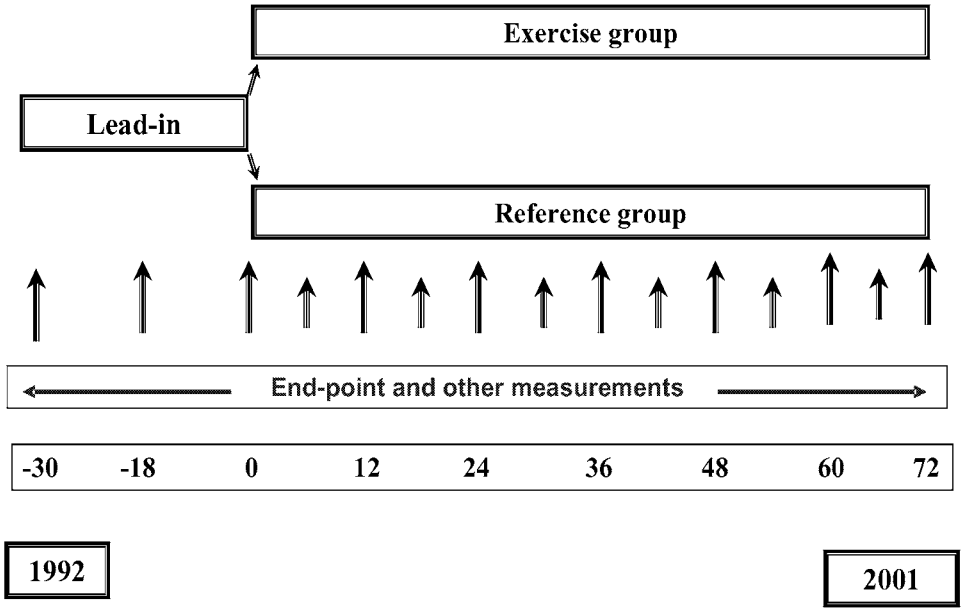


Figure 5. The DNASCO study design. On the axis of end-point and other measurements higher arrows include ergospirometry, carotid ultrasonography and blood samples, while lower arrows include carotid ultrasonography and anthropometric measurements. On the time axis, the cross-sectional studies (I and II) were performed at the points of -30 and -18 months and the follow-up study (III) encompassed the period between 0 to 72 months.

4.2. Patients with coronary artery disease (Studies IV and V)

Fifty-two patients admitted to hospital either for elective coronary angiography or elective coronary angioplasty were recruited for this trial. The inclusion criteria were age > 18 years, stable angina pectoris (NYHA II-III), previously positive exercise test (ST-depression ≥ 0.15 mV), ≥ 50 % stenosis in at least one of the main coronaries (angiogram) and informed consent to take part in the study. The exclusion criteria were unstable angina, congestive heart failure, atypical chest pain, undiagnostic electrocardiogram (bundle branch block, left ventricular hypertrophy with ST-strain, anterior Q-wave or marked T-wave inversions at rest, Wolff-Parkinson-White syndrome with delta-wave), any difficulties to perform bicycle ergometer test, use of digoxin and presence of diabetes. The patients underwent two successive exercise tests and they were randomized into four groups, based on different resting periods between the two tests (15, 30, 60 and 120 min after the recovery from the first ischemia episode) (Study III).

The patients in study IV consisted of that same original patient population. Since only four women were included in the primary study, they were excluded from the second part of the study investigating autonomic regulation in warm-up phenomenon to avoid any possible gender driven bias in heart rate variability. Therefore, fifty-one males with coronary artery disease formed the study population in study IV. Since there was one case of missing ambulatory ECG data, fifty patients were included in the final analyses of HRV and HRT. The baseline characteristics of the patients are presented in Table 4 and the cardiovascular medication being used by the subjects in the study on HRV and HRT (IV) is presented in Table 5.

Table 4. Baseline characteristics of the patients in studies I –V.

	Study I	Study II	Study III	Study IV	Study V
Number of subjects	212	163	100	52	51
Male (%)	100	100	100	92	100
Age (yr)	55.1 ± 2.9	55.3 ± 3.0	57.4 ± 3.0	59.3 ± 8.6	59.2 ± 8.5
BMI (kg/m2)	27.0 ± 3.7	NA	27.1 ± 3.6	26.6 ± 2.9	26.7 ± 2.9
VO2max (ml/kg/min)	29.6 ± 6.3	29.6 ± 5.9	31.2 ± 7.1	26.1 ± 4.8*	26.3 ± 4.9*
AAT (ml/kg/min)	23.7 ± 5.5	26.6 ± 5.6	22.5 ± 5.9	NA	NA
VAT (ml/kg/min)	14.7 ± 3.4	17.8 ± 3.7	14.0 ± 3.5	NA	NA
Waist to hip ratio	0.97 ± 0.05	0.97 ± 0.05	0.97 ± 0.05	NA	NA

Presented as percentage of subjects or mean ± SD. BMI = body mass index; VO2max = maximal oxygen uptake, AAT = anaerobic threshold; VAT = ventilatory aerobic threshold; NA = value not available. * indirect estimates.

Table 5. Cardiovascular medication of the subjects in studies on HRV and HRT.

	Study III (N = 100)	Study V (N = 50)
β-blockers	18 (18%)	47 (94%)
Acetylsalicylic acid	28 (28%) *	48 (96%)
Long-acting nitrates	6 (6%)	29 (58%)
Calcium-channel blockers	7 (7%)	14 (28%)
ACE-inhibitors	8 (8%)	8 (16%)
Lipid-lowering agents	4 (4%)	37 (74%)

* after the six-year intervention

5. METHODS

5.1. Assessment of physical activity

Current physical activity of the subjects was determined by the Stanford seven-day recall interview (Sallis et al. 1985). On the basis of exercise culture in Eastern-Finland cross-country skiing and long-distance skating were added to the interview list. The subjects were asked to recall the time spent sleeping and in mild, moderate and heavy physical activities during the previous seven days. Energy expenditure was assessed as metabolic equivalents (MET), which is a calculated ratio of work metabolic rate / rest metabolic rate. Examples of mild activities (energy expenditure 3.0 – 5.0 MET) included brisk walking, golfing and bicycling not hard enough to cause breathlessness. Moderate activities (5.1 – 6.9 MET) included cross-country skiing, swimming and dancing with sufficient intensity to cause sweating and / or breathlessness. Heavy activities (≥ 7.0 MET) included jogging and cross-country skiing at a sufficient intensity to cause profound sweating and / or breathlessness. Also recovery from very hard exercise had to take an extended time period. Very mild physical activities (1.0 – 2.9 MET) were also estimated (Table 6).

Table 6. MET values used to estimate energy expenditure

	MET
Sleep	1
Very mild activity	1.5
Mild activity	4
Moderate activity	6
Heavy activity	10

MET = metabolic equivalent.

Average daily physical activity index was then determined by multiplying MET values by the hours spent in each of the presented five categories of physical activity. Resting energy expenditure (REE) was calculated from the following equation: (11.6 x weight in kg) + 879 (World Health Organization 1985).

Daily energy expenditure (kcal / kg / day) was estimated by multiplying this REE by the daily physical activity index. In addition to total energy expenditure (TEE), also energy expenditure in physical activity (mild + moderate + heavy activity) and energy expenditure separately in all three categories of physical activity were calculated. Daily REE (kcal / day) was used as an estimate of physical inactivity.

5.2. Dietary intake

Detailed registration of habitual diet was assessed by using a four-day food record. The same investigator instructed the men how to keep the food records and checked them together with participants for completeness and accuracy after the recording period. Portion sizes were estimated using a picture booklet or household measurement units. Records were analyzed using custom-built software (MicroNutrica).

5.3. Anthropometry and determination of body fatness

Body fatness was evaluated on the basis of the sum of skinfolds, which were measured as millimeters with a standard device including four standard sites (biceps, triceps, subscapularis and suprailiac). Other anthropometric measurements included weight and circumferences of waist and hip. Weight was measured with a digital scale in light clothing without shoes. BMI was calculated dividing body weight by the height squared (kg/m2). Waist circumference was determined from the halfway level between lower rib margin and the iliac crest. Hip circumference was determined from the greater trochanter level. The waist to hip ratio was calculated for each subject.

5.4. Smoking as a cardiovascular risk factor

Smoking habits and number of cigarettes per day (smokers) were determined during the interview. In statistical analyses it was used as a basic binary class variable (smoker / nonsmoker).

5.5. Office measurement of blood pressure

Blood pressure (BP) was measured using a random zero device with a cuff size of 52 x 14 cm. After a resting period of 15 min, BP was measured three times within a 5 min interval in the supine position. After that two measurements were performed in the standing position (the first immediately after standing up and the second after 2 min). The last measurement was performed after the subject had been sitting for 2 min.

5.6. Laboratory analyses

Venous blood samples were taken after a 12-hour overnight fast and a 30-min resting period in the supine position between 07:30 – 10:00 a.m. without the use of stasis. The subjects were advised not to take any non-steroidal anti-inflammatory drugs (NSAID) during the previous 7 days. In the case of acute respiratory infection, blood samples were drawn at least one week after the disappearance of symptoms. Lipoproteins were fractionated from fresh serum samples by ultracentrifugation and selective precipitation. In addition to the determination of serum HDL cholesterol, its subfractions HDL2 and HDL3 were also determined. Cholesterol was measured from serum and lipoprotein fractions using an enzymatic cholesterol oxidase method and serum triglycerides were also determined enzymatically (Boehringer Mannheim Gmb, Germany). Serum apolipoproteins (A-I, A-II and B) were determined immunoturbidimetrically (KONE Instruments, Espoo Finland and Orion Diagnostica, Espoo, Finland). Plasma fibrinogen was measured from a fresh sample using the thrombin time method (Baxter Dade, Miami, Fl, USA). Plasma insulin was determined radioimmunologically Pharmacia Diagnostics Ab, Uppsala, Sweden).

5.7. Ultrasonography of carotid arteries

Two certified sonographers performed the carotid ultrasound examinations. B-mode ultrasound imaging protocol was designed to ensure the valid and reliable identification of arterial carotid references and the definition of near and far wall interfaces. The carotid artery was divided into two segments based on arterial anatomy and geometry. These segments were distal common carotid artery and the carotid bifurcation, i.e. the bulb. In the horizontal view, the major anatomical features defining these two segments

were the proximal origin of the bulb and the tip of the flow divider separating internal and external carotid arteries. In longitudinal images, the specific anatomical boundaries defining the intima-media thickness (IMT) were the adventitia-media and intima-lumen interfaces in the near wall and oppositely lumen-intima and media-adventitia interfaces in the far wall. The examinations with the ultrasound device (Biosound Phase Two, Biosound Inc., Indianapolis, In, USA) were recorded on video tapes and a separate computerized reading station was used to analyze the recordings.

5.8. Maximal bicycle ergometer test with respiratory gas analyses

Bicycle ergometer stress test was performed using a protocol of incremental workload by 20 watts stepwise at every one minute interval. ECG was registered continuously using an electrocardiograph designed for stress testing (Marquette Centra, Marquette Electronics Inc., Milwaukee, Wis, USA). Standard chest leads and limb leads (Mason-Likar modification) were registered. In addition to continuous monitoring ECG was also recorded every minute during exercise and up to seven minutes during recovery. ST-segment depression was measured 80 msec after the J-point using computerized analysis. Whenever net ST-segment depression compared to baseline values exceeded the level of 1 mm (0.1 mV), it was considered as being ischemic. Systolic blood pressure was measured by an automated device.

Ventilation and oxygen uptake were monitored directly using respiratory gas analyses covering the whole test protocol. The test was continued until either subjective or objective maximal level was attained. The subjective maximum level was determined by using a Borg's scale (Borg et al. 1982). The objective maximum level was predetermined as an increase in oxygen consumption which was less than 150 ml/min in spite of the increase in work load. The ventilatory aerobic threshold (VAT) was determined on the basis of the first and characteristic nonlinear increase in minute ventilation with a less prominent increase in end-tidal oxygen consumption and respiratory quotient (RQ) simultaneously. The anaerobic threshold was determined on the basis of the later steep increase in minute ventilation.

5.9. Exercise intervention protocol

The subjects, who were randomized into the exercise group, were instructed to perform walking, jogging, swimming, bicycling and cross-country skiing as the main methods of aerobic exercise according to a predefined progressive program with a preliminary warm-up for a period of 3 months at the beginning of the intervention (Table 7).

Table 7. The exercise program of the DNASCO study.

	Exercise duration	Times per week	Intensity (of VO_2max)
0 – 3 months	30 – 45 min	3	40 – 60 %
3 months – 6 years	45 – 60 min	5	40 – 60%

VO_2max = maximal oxygen consumption.

As presented the intensity of training was individually constructed and it was equally related to maximal cardiorespiratory performance in every subject. The intensity of 40 – 60% of the VO_2max was selected to correspond to the VAT level. The men in the exercise groups had heart rate monitors to optimize their adherence to the prescribed heart rate during training. The men performed the program on their own, but reported all of their activities in the training diary. The exercise physiologist checked the diary together with each participant at 6-month intervals. As stated in the regulations of the Ethics Committee, the subjects in the control group were allowed to choose whether to engage in exercise training or not. However, no special efforts were made to change the habitual physical activity of these subjects and they were not obliged to keep an exercise diary and in that way they differed from their counterparts in the training group.

5.10. Repeated exercise testing

5.10.1. Protocol and analyzed parameters

The patients underwent two successive bicycle ergometer tests before the invasive procedures. Patients continued to take any prescribed antianginal medication. The starting load was 20 W and it was increased stepwise by 20 W at one minute intervals. The first exercise test was discontinued whenever symptoms limited further exercise or the patient was unable to maintain the cycling rate of 60 rpm in the ergometer. The resting period (15 – 120 min) was taken to begin after the disappearance of ischemia (ST-depression < 0.05 mV). The exercise protocols in both tests were identical. ECG was registered continuously using an electrocardiograph designed for stress testing (Marquette Centra, Marquette Electronics Inc., Milwaukee, Wis, USA). Standard chest leads and limb leads (Mason-Likar modification) were used. ST-segment depression was measured 60 msec after the J-point using computerized analysis. The values were checked manually and corrected when appropriate. Blood pressure was measured manually at least every other minute during exercise.

During both exercise tests (including pre-test, exercise and recovery measurements) the following parameters were analyzed: 1) time required for the appearance of 0.1 mV ST-depression, 2) maximal intensity (subjective) of anginal pain using Borg´s scale (Borg et al. 1981), 3) maximal ST-segment depression, 4) the time required for the appearance and the disappearance of angina pectoris, 5) time required for the ST-depression to return to the level of < 0.05 mV, 6) ST/HR slope (μV/bpm) during exercise, 7) Wlast4, i.e. the mean work load during the last four minutes of exercise, and total duration of exercise, 8) calculated maximal oxygen consumption, 9) ischemic burden (ST-depression in mV · duration in min) covering the time period from the appearance to the disappearance of 0.1 mV ST-depression, 10) heart rate, blood pressure and rate-pressure product at one minute intervals.

5.10.2. Evaluation of adaptation to ischemia

The criteria for the appearance of the warm-up phenomenon were predetermined as follows: the time to 0.1 mV ST-depression had to be lengthened by at least 1 min or the maximal ST-depression had to stay below the level of 0.1 mV during the second test.

5.11. Cardiac catheterization

All patients in studies III and IV underwent cardiac catheterization on the day following the exercise testing. Left ventriculography was performed to determine left ventricular ejection fraction (LVEF). Coronary angiography was performed in at least six projections with cranial and caudal angulated views. The view with the best visualization of the lesion was selected for measurement of the maximal severity of the coronary artery stenoses. Determination of stenoses was done visually by an experienced radiologist and/or cardiologist, and diameter stenoses of ≥ 50 % were considered significant. Ipsi- and contralateral collateral channels were also registered. To get a better estimate of the extent of coronary artery disease, a coronary score was calculated by the method introduced by Winkelmann et al. (1994). This scoring method provides a weighting to the most severe stenotic lesions according to their exact location in different parts of the main coronary arteries. The scoring was done blinded to the results of the exercise tests.

5.12. Ambulatory electrocardiograms

In study IV, ambulatory ECG recordings were made using digital recorders (Oxford Medilog Excel FD-3, Oxford Instruments Ltd, UK), the registration covering the whole test protocol. In study V, 24-hour ECG registrations were performed using analog tape-recorders (Marquette Electronics Inc., Milwaukee WI, U.S.A.) basically due to the non-availability of digital recorders at the beginning of the DNASCO study in 1995. To avoid the possibility of equipment driven bias, the same analog recorders were used for registrations after the six year follow-up period. In both studies IV and V, the initial analyses of the ECG were performed using an automated procedure (Oxford Medilog Iris, Oxford Instruments Ltd, UK) and the reliability of the classified ECG templates was checked manually and corrected in appropriate cases. Annotated RRI data was then transformed into ASCII-form and the final analyses were done using custom-built software designed for a variety of time series (WinCPRS version 1.156, Absolute Aliens Co., Finland).

HRT was determined by a signal averaging method from single VPCs fulfilling the following two criteria: coupling interval within 80 % and compensatory pause longer

than 110 % of the mean of the five preceding RRIs. These five preceding and also the fifteen following RRIs had to be free of ectopic complexes. Two different parameters, turbulence onset (TO) and turbulence slope (TS) were computed and only entire recordings were used. This method has been previously described in detail (Schmidt et al. 1996, 1999).

After determination of HRT, all RRIs adjacent to VPCs and supraventricular premature complexes (SVPC) were edited (see below) before the determination of HRV parameters. For spectral HRV parameters, interpolation was used as an editing method to maintain the continuous nature of frequency domain measures. In the case of all other parameters, a deletion procedure was used to remove the ectopic RRIs. A recent report has claimed that in frequency domain analysis, interpolation performs better leading to smaller errors in the editing process especially of long-term but also of short-term registrations (Salo et al. 2001). The following time domain indices were determined: mean of all normal RRIs, SDNN (standard deviation of normal RRIs), RMSSD (root mean square of successive difference of normal RRIs) and pNN50 (percentage of RRIs differing by more than 50 ms from the previous RRI). In frequency domain analysis, the power spectrum was divided into four different bands. The following variables were calculated: total power ($\leq$ 0.4 Hz), ultra low frequency (ULF) power ($\leq$ 0.003 Hz), very low frequency (VLF) power (0.003 – 0.04 Hz), low frequency (LF) power (0.04 – 0.15 Hz) and high frequency (HF) power (0.15 – 0.4 Hz) in ms^2 (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology 1996). Logarithmic (ln) transformations were performed due to the abnormal distribution of the power spectral variables. The ratio of LF- to HF-power was calculated from their original power values.

In study IV, the same editing protocol and HRV analyses were performed using the whole registrations and four separate periods of five minutes' duration. In study V, the editing protocol and time and frequency domain analyses of 24-hour HRV were identical to those used in study IV. In addition to time and frequency domain HRV indices, the following nonlinear parameters of HRV were also determined in study V: fractal dimension (FD), the short-term and the long-term scaling exponent alpha ($\alpha 1$ and $\alpha 2$). In addition, the Poincaré plot analysis representing also a geometrical measure of HRV was performed (calculated parameters SD1 and SD2).

During those short-term stationary phases, the patients rested silently in the supine position with a spontaneous breathing frequency (pre- and post-test one and two). The post-test phases started immediately after the disappearance of ischemia (ST-depression less than 0.05 mV and no symptoms). The proportions of edited beats were less than 10 % in all registration periods. Exercise-induced VPCs and SVPCs during both tests and also the cumulative number of VPCs during the entire recordings were calculated. The determination of VPC morphologies was based on a computerized classification of QRS morphology after manual inspection and correction of the ECG signal. The primary purpose of the entire recordings covering the whole test protocol was to evaluate more thoroughly global heart rate variability in conditions resembling normal daily activities in miniature containing both rest and physical exercise with consecutive periods of ischemia.

5.13. Statistical methods

In Study I, student's t-test was used to analyze the differences in normally distributed variables between the diseased and the healthy men. Associations between physical activity, cardiorespiratory fitness, body fatness and CAD risk factors as well as the test-related correlations were analyzed by Pearson's correlation coefficient. Due to a skewed distribution, all analyses including energy expenditure in mild, moderate or heavy physical activity were done using nonparametric tests (Spearman's rank-order correlations, Mann-Whitney U-test). All analyses were adjusted for age and 95 % confidence intervals were also determined. In the correlation analyses, the level of statistical significance was set at P-value < 0.01.

In Study II, distributions of serum triglycerides, VLDL cholesterol and plasma insulin were skewed so logarithmic transformations of these parameters were performed. Since the age of the subjects was strictly defined, age was taken as a dummy variable in the statistical analyses. Pearson's correlation coefficients and analysis of covariances (ANCOVA) were used as continuous variables and chi-square test for categorical variables. ANCOVA was performed in two stages. First of all, the potential confounding variables were taken into the model separately. Secondly, those covariates showing a P-value < 0.1 were brought into the model simultaneously, with 95 % confidence intervals were also being determined.

In Study III, two-way analysis of variance (ANOVA) for repeated measures was used to compare changes in HRV and HRT parameters, VAT and VO2max between the exercise and reference groups. Correlation coefficients were determined between HRV and HRT parameters and both VAT and VO2max. Furthermore, the differences (intervention–baseline) for the same parameters were calculated for each patient and correlation coefficients were determined between the delta values. As in Study IV, the parametric Pearson's correlation coefficient was used in cases of normality of the measured parameters and in cases with an abnormal distribution, the nonparametric Spearman's correlation coefficient was used. Similarly, bivariate correlations between HRT and HRV parameters and their delta values were calculated.

In Study IV, the differences for the time-dependent changes in hemodynamic and ischemia parameters (exercise 2 – exercise 1) were calculated for each patient and the means were compared between groups 1 – 4. One-way analysis of variance (ANOVA) was used in the case of both normality and homogeneity of variances, otherwise nonparametric Kruskal-Wallis test was used. Comparisons between the groups were also done by Scheffé´s post-hoc testing in appropriate cases. The comparisons within groups were done using paired t-test (in the case of normality) or the nonparametric exact Wilcoxon test. Normality was tested using Shapiro-Wilk test. Crosstabulation and chi-square test were used when comparing the number of patients demonstrating warm-up phenomenon in the groups. Finally, the patients were divided into two groups on the basis of the severity of their CAD and pre-existing CAD risk factors such as serum cholesterol levels. Chi-square test was used when comparing patients with and without ischemia-adaptation in the groups.

In Study V, one-way analysis of variance (ANOVA) and crosstabulation with chi-square test were used when comparing the clinical characteristics between the groups. In the analysis of the entire ambulatory ECG recordings, the mean values of HRV and HRT parameters were compared between the groups using ANOVA in the case of both normality and homogeneity of variances, otherwise the nonparametric Kruskal-Wallis test was used. In the analysis of the four short-term registration periods at supine rest, two-way analysis of variance for repeated measures was used. The normality of the distribution of the variables was tested using the one-sample Kolmogorov-Smirnov test. The differences for the time-dependent changes in hemodynamic and ischemia parameters were calculated for each patient and correlation coefficients between those

delta values and HRV variables were determined. As in Studies III and IV, statistical significance (two-tailed tests) was set at 5 %.

6. RESULTS

6.1. Basic characteristics of middle-aged men with and without chronic diseases (Study I)

At baseline, there were 69 subjects in the group of healthy men and 136 in the group of men with chronic diseases. Generally, healthy subjects appeared to be significantly younger than men with chronic diseases (mean 54.1 yr. and 55.7 yr., respectively, $p < 0.001$). Two out of three measures of cardiorespiratory fitness (i.e. VO2max and anaerobic threshold) tended to be higher in healthy men already at the baseline, but after the one-year follow-up both determinants of exercise performance were significantly higher in the healthy subjects ($p < 0.001$ for both). Smoking habits, measures of anthropometry, energy expenditure and concentrations of serum lipoproteins and plasma fibrinogen were similar between the groups.

6.2. Correlation between physical activity and cardiorespiratory fitness, body fatness and CAD risk factors in healthy men (Study I)

Energy expenditure at rest (REE) had a significant negative correlation with VO2max and anaerobic threshold both at the baseline and after the one-year follow-up ($r = -0.46$ and -0.40 for VO2max and $r = -0.43$ and -0.42 for anaerobic threshold, respectively). No significant correlation between REE and aerobic threshold was found despite there being a similar tendency ($r = -0.27$ and -0.31). REE also correlated positively with the body fatness assessed by the sum of skinfolds and waist-to-hip ratio (W/H) at both examinations ($r = 0.33$ and 0.44 for skinfolds and $r = 0.31$ and 0.39 for W/H). At the baseline, total energy expenditure (TEE) correlated negatively with the sum of skinfolds but not with W/H ($r = -0.35$, $p < 0.01$). Furthermore, no association between TEE and measures of cardiorespiratory fitness could be reported. TEE did not correlate with other CAD risk factors. However, an inverse correlation between REE and HDL-cholesterol ($r = -0.33$, $p < 0.01$) and a direct correlation between energy expenditure in physical activity and LDL-cholesterol ($r = 0.33$, $p < 0.01$) was documented. All correlation coefficients were age-adjusted.

6.3. Correlation between physical activity and cardiorespiratory fitness, body fatness and CAD risk factors in men with chronic diseases (Study I)

In men with chronic diseases, TEE and energy expenditure in physical activity correlated positively, whereas REE correlated negatively with VO2max, and with both anaerobic and aerobic threshold at baseline and after the follow-up in contrast to the findings in the healthy group. A more detailed analysis showed that energy expenditure in moderate physical activity associated directly with all measures of cardiorespiratory fitness. However, the significant baseline correlation between cardiorespiratory fitness and energy expenditure at heavy physical activity had vanished after the one-year follow-up period. TEE and energy expenditure at physical activity associated inversely and REE directly with body fatness (i.e. the sum of skinfolds and W/H) in both examinations. Furthermore, at the baseline, TEE correlated negatively and REE positively with the concentrations of plasma fibrinogen and serum triglycerides, whereas after one year, a significant correlation was seen only with serum triglycerides. No significant correlation was found between any of the determined energy expenditure values and serum total and LDL-cholesterol levels, while HDL-cholesterol correlated directly with energy expenditure at heavy physical activity at baseline and TEE after the follow-up and inversely with REE at the end (Table 8).

6.4. One-year consistency of the measurements (Study I)

Repetitiveness of measurements of energy expenditure (excluding energy expenditure in heavy physical activity in healthy men), cardiorespiratory fitness, body fatness and CAD risk factors was high in both groups of middle-aged men. The ranges for correlation coefficients between two examinations varied from 0.41 to 0.91 in healthy and from 0.33 to 0.87 in men with chronic diseases, the poorest repeatability concerning energy expenditure in moderate physical activity and the best reproducibility was found for the sum of skinfolds, this being found in both groups. The relative difference between two measurements of TEE was 5.6% and the respective percentages for REE and energy expenditure in physical activity were 2.4% and 16.8%, respectively.

Table 8. Correlation coefficients between physical activity and cardiorespiratory fitness, body fatness and CAD risk factors in men with chronic diseases.

Baseline examination (N = 136)

	TEE	EE-ph	EE-mp	EE-hp	REE
VO2max	0.45**	0.39**	0.35**	0.28**	-0.38**
AAT	0.42**	0.36**	0.33*	0.26*	-0.36**
AT	0.40**	0.34**	0.29**	0.26*	-0.42**
SSF	-0.51**	-0.42**	-0.27*	-0.19	0.45**
W/H	-0.34**	-0.23*	-0.09	-0.13	0.41**
Fibr	-0.32**	-0.30**	-0.12	-0.17	0.25*
Trigly	-0.26*	-0.21	-0.14	-0.19	0.24*
Chol	0.07	0.06	0.02	0.15	-0.04
LDL	0.07	0.06	0.02	0.09	-0.03
HDL	0.18	0.12	0.03	0.25*	-0.19

1-year follow-up examination (N = 122)

	TEE	EE-ph	EE-mp	EE-hp	REE
VO2max	0.45**	0.36**	0.38**	0.20	-0.40**
AAT	0.40**	0.32**	0.32**	0.11	-0.38**
AT	0.35**	0.28**	0.32**	0.18	-0.32**
SSF	-0.50**	-0.34**	-0.12	-0.28*	0.43**
W/H	-0.42**	-0.26*	-0.27*	-0.19	0.36**
Fibr	-0.18	-0.12	-0.07	-0.10	0.21
Trigly	-0.24*	-0.15	-0.09	-0.18	0.24*
Chol	0.20	0.22	0.10	0.14	-0.13
LDL	0.18	0.21	0.05	0.17	-0.08
HDL	0.30*	0.22	0.17	0.17	-0.29**

* $p < 0.01$; ** $p < 0.001$. TEE = Total energy expenditure; EE-ph = Energy expenditure in physical activity; EE-mp = Energy expenditure in moderate physical activity; EE-hp = Energy expenditure in heavy physical activity; REE = Energy expenditure at rest; VO2max = Maximal oxygen consumption; AAT = Anaerobic threshold; AT = Aerobic threshold; SSF = Sum of skinfolds; W/H = Waist-to-hip ratio; Fibr = Plasma fibrinogen; Trigly = Serum triglycerides; Chol = Serum total cholesterol; LDL = Serum low density lipoprotein cholesterol; HDL = Serum high density lipoprotein cholesterol

6.5. Cardiovascular risk factors and cardiorespiratory fitness in men with and without cardiovascular disease (Study II)

59 subjects were clinically healthy, 61 had cardiovascular disease (CVD) and 43 had some non-cardiovascular disease. Men with CVD had a higher BMI (mean 27.7 kg/m2, 95% CI 26.4 – 28.6) compared to men without CVD (mean 26.0 kg/m2, 95% CI 25.4 – 26.7) ($p = 0.022$). The waist to hip ratio did not differ markedly between the groups. Basically, habitual diet was quite similar in both groups except that saturated fat intake was lower in men with CVD compared to the other group ($p = 0.043$).

Men with CVD had higher levels of plasma insulin (10.1 µU/ml (CI 8.3 – 11.9) vs. 7.8 (6.8 – 8.7), $p = 0.026$), serum triglyceride (1.44 mmol/l (1.25 – 1.63) vs. 1.20 (1.08

– 1.33), p = 0.014) and VLDL cholesterol (0.59 mmol/l (0.49 – 0.69) vs. 0.48 (0.42 – 0.55), p = 0.047) and lower apolipoprotein A-I (1.26 g/l (1.21 – 1.30) vs. 1.32 (1.29 – 1.36), p = 0.031) than men without CVD. Other serum lipoproteins and apolipoproteins and plasma fibrinogen were similar in both groups. Furthermore, men with CVD had higher diastolic blood pressure levels in the supine (85 mmHg (82 –88) vs. 81 (80 –83), p = 0.01), standing (93 mmHg (91 – 96) vs. 90 (88 – 92), p = 0.033) and sitting (89 mmHg (87 – 92) vs. 86 (84 – 88), p = 0.021) positions compared to men without CVD. The same was true also for systolic blood pressure in the supine (136 mmHg (132 – 140) vs. 128 (125 – 130), p < 0.001) and sitting (138 mmHg (134 – 142) vs. 133 (130 – 136), p = 0.032) positions. Systolic blood pressure showed no difference between groups in the standing position.

In the ergospirometry test, men with CVD had lower maximal oxygen consumption (27.0 ml/kg/min; 25.5 – 28.6) compared to men without CVD (31.2 ml/kg/min; 30.1 – 32.2) (p < 0.001). Similar findings were observed in the assessment of both aerobic and anaerobic thresholds.

6.6. Relationship between carotid atherosclerosis and exercise induced ischemia (Study II)

In ECG recorded during ergospirometry, ST-segment depression of 1.0 mm or more was documented in 77 subjects (47%). In 19 men, STD even exceeded beyond the level of 3.0 mm (25 % of these suspected ischemic findings). In 70 subjects, the STD changes were seen in lateral chest leads (C 5-6) and only 7 men presented purely inferior ECG changes. All subjects were then divided into 3 categories according to the stress test ECG results: No major changes, STD 1.0 – 3.0 mm and STD > 3.0 mm. These groups did not differ in VO2max or exercise energy expenditure. When adjusted for all cardiovascular medications, subjects in the most severe STD tertile showed significantly thicker IMT in the carotid artery bifurcation than other groups (p for trend 0.048). No significant differences were observed in the common carotid IMT.

6.7. Relationship between cardiorespiratory fitness and cardiovascular risk factors (Study II)

In the whole study population, maximal oxygen uptake associated significantly and inversely with VLDL cholesterol (r = -0.27), triglycerides (r = -0.41), apolipoprotein B (r = -0.23), insulin (r = -0.49) and fibrinogen (r = -0.24). Furthermore, it associated significantly and directly with HDL cholesterol (r = 0.43), HDL2 cholesterol (r = 0.38), HDL3 cholesterol (r = 0.22) and apolipoprotein A-I (r = 0.33). For further evaluation, the subjects were divided into quartiles of VO2max. The cut-off points were as follows: Quartile I < 25.9 ml/kg/min, quartile II 25.9 – 29.4 ml/kg/min, quartile III 29.4 – 33.3 ml/kg/min and quartile IV > 33.3 ml/kg/min. Determined risk factor profiles according to the quartiles of VO2max are presented in Table 9.

Table 9. Cardiovascular risk factor profiles in the quartiles of maximal oxygen consumption.

	I	II	III	IV	P for trend
Chol (mmol/l)	5.42	5.61	5.51	5.41	NS
VLDL (mmol/l)	0.64	0.56	0.53	0.36	0.018
LDL (mmol/l)	3.65	3.90	3.77	3.66	NS
HDL (mmol/l)	1.13	1.15	1.22	1.40	<0.001
HDL2 (mmol/l)	0.76	0.77	0.83	0.99	<0.001
HDL3 (mmol/l)	0.37	0.38	0.39	0.41	NS
Trigly (mmol/l)	1.58	1.33	1.36	0.89	<0.001
Apo A-I (g/l)	1.26	1.25	1.30	1.39	0.001
Apo A-II (g/l)	0.29	0.28	0.29	0.28	NS
Apo B (g/l)	1.08	1.08	1.05	0.93	0.007
P-Fibr (g/l)	3.41	3.35	3.24	3.03	0.011
P-Ins (μU/ml)	11.7	8.7	7.8	5.2	<0.001

Chol = Serum cholesterol; VLDL = Serum very low density lipoprotein cholesterol; LDL = Serum low density lipoprotein cholesterol; HDL = Serum high density lipoprotein cholesterol; HDL2 and HDL3 = Subfractions of serum high density lipoprotein cholesterol; Trigly = Serum triglycerides; Apo A-I = Apolipoprotein A-I; Apo A-II = Apolipoprotein A-II; Apo B = Apolipoprotein B; P-Fibr = Plasma fibrinogen; P-Ins = Plasma insulin. Presented as mean values.

6.8. Relationship between cardiorespiratory fitness and carotid atherosclerosis (Study II)

In the whole study population VO2max and anaerobic threshold were inversely related to bifurcation IMT ($r = -0.31$, $p < 0.001$ and $r = -0.26$, $p = 0.001$, respectively), whereas in the case of aerobic threshold result did not reach statistical significance ($r = -0.14$, $p = 0.08$). IMT of the common carotid artery was not associated with cardiorespiratory fitness.

The mean values and 95% CI of the carotid bifurcation IMT in the quartiles of VO2max are presented in Table 10. In the highest fitness quartile, the mean IMT was 0.44 mm (95% CI 0.22 – 0.67), representing 88% of the SD, lower than that of the men in the lowest fitness quartile, and 0.28 mm (95% CI 0.10 – 0.47), representing 56% of the SD, lower than that of the men in the second lowest VO2max quartile (p for both < 0.001). These differences remained significant after controlling for age, plasma fibrinogen, plasma insulin, serum LDL and HDL cholesterol, systolic blood pressure, smoking, body mass index, exercise induced STD, current health status (with or without CVD) and dietary saturated fat intake. The analyses were repeated separately in both groups with and without CVD but the results remained similar. When VO2max quartile and CVD category were entered as grouping variables, only VO2max had significant main effects ($F = 4.760$, $p = 0.003$). In this analysis, there was no evidence of interaction between cardiorespiratory fitness and history of CVD ($F = 0.751$, $p = 0.610$).

Table 10. The mean values (95% CI) of carotid bifurcation intima-media thickness in the quartiles of maximal oxygen consumption.

	I	II	III	IV	
IMT (Ua)	1.95 (1.75-2.16)	1.79 (1.63-1.95)	1.68 (1.57-1.79)	1.51 (1.41-1.61)	*
IMT (Ca)	1.89 (1.71-2.07)	1.80 (1.63-1.96)	1.69 (1.52-1.86)	1.56 (1.38-1.73)	#

* p for trend < 0.001; # p for trend < 0.05. IMT = Intima-media thickness; Ua = Unadjusted; Ca = Covariate adjusted (for age, ST-segment depression, systolic blood pressure, LDL cholesterol saturated fat intake and health status i.e. categories of cardiovascular disease or not).

6.9. Changes in cardiorespiratory fitness during the six-year exercise intervention (Study III)

In eligible subjects with reliable Holter data at both examination points, VAT increased significantly by 16 % in the exercise group during the intervention indicative of an improved level of submaximal fitness. VO2max tended to decrease in both groups reduction being more prominent in the reference group. The results of measures of cardiorespiratory fitness are shown in Figure 6.

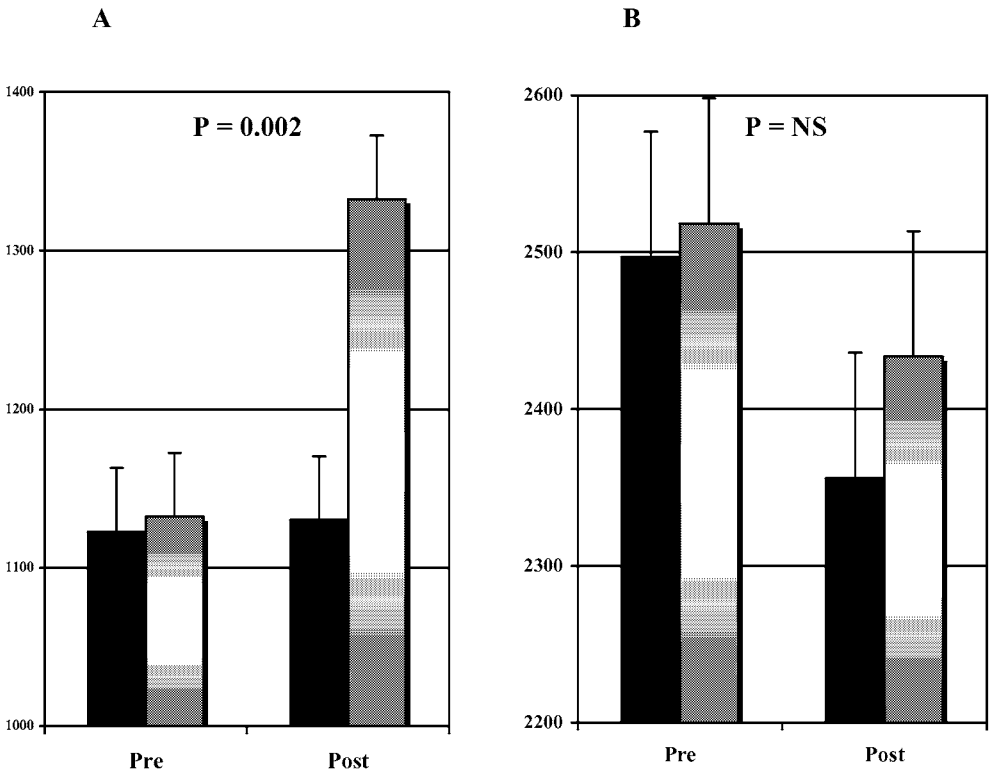


Figure 6. Measures of cardiorespiratory fitness at baseline and after the six-year exercise intervention. **A)** VAT (ml/min), **B)** VO2max (ml/min). Presented as mean ± SEM. Black bars = reference group; gray bars = exercise group; p for the delta values between groups.

6.10. Regular exercise training and cardiac autonomic nervous function (Study III)

In the six-year exercise intervention, HRV parameters did not differ significantly between the groups at baseline or after intervention. However, the changes in HRV parameters were not significantly different between the groups during the six years. Slight increases in only a few HRV parameters were observed in both groups. Furthermore, neither the HRT parameters at both examinations nor the changes in HRT during six-year intervention differed significantly between the groups.

In addition to comparison between the groups, all subjects were studied as one group to investigate the relationships between measured cardiorespiratory fitness and HRV and HRT. SDNN, Poincaré plot SD2 and most frequency domain indices correlated significantly with VAT at both examinations. Similarly, a significant correlation was seen between the delta values for the same HRV parameters and VAT during the intervention (Table 11). No significant correlation was found between the changes in HRV parameters and the change in VO2max. The change in TS correlated significantly with the changes in most HRV variables (Table 11). The change in TO correlated significantly with the changes in three frequency domain indices. However, neither the change in TO nor that in TS correlated with the changes in VAT or VO2max.

Table 11. Correlation coefficients between the changes in VAT and HRV and between the changes in TS and HRV during the six-year exercise intervention.

	Δ VAT (N = 90)	Δ TS (N = 73)
Δ mean RRI	0.04	0.18
Δ SDNN	0.37 ***	0.23
Δ RMSSD	0.13	0.37 **
Δ pNN50	0.14	0.32 **
Δ total power (ln)	0.30 **	0.31 **
Δ ULF power (ln)	0.30 **	0.20
Δ VLF power (ln)	0.24 *	0.32 **
Δ LF power (ln)	0.17	0.53 ****
Δ HF power (ln)	0.24 *	0.47 ****
Δ LF/HF ratio	-0.12	0.05
Δ FD		0.27 *
Δ α1		-0.21
Δ α2		-0.10
Δ SD1 (Poincaré plot)	0.15	0.43 ***
Δ SD2 (Poincaré plot)	0.37 ***	0.20

**** $p < 0.0001$, *** $p < 0.001$, ** $p < 0.01$ and * $p < 0.05$. Δ = difference (post – pre); VAT = ventilatory aerobic threshold; TS = turbulence slope; α1 = short-term scaling exponent; α2 = long-term scaling exponent; FD = fractal dimension; HF = high frequency; LF = low frequency; pNN50 = percentage of RRIs differing > 50 ms from the previous RRI; RMSSD = root mean square of successive difference of normal RRIs; RRI = RR-interval; SDNN = standard deviation of normal RRIs; ULF = ultra low frequency; VLF = very low frequency.

6.11. The incidence of warm-up phenomenon as a function of resting time (Study IV)

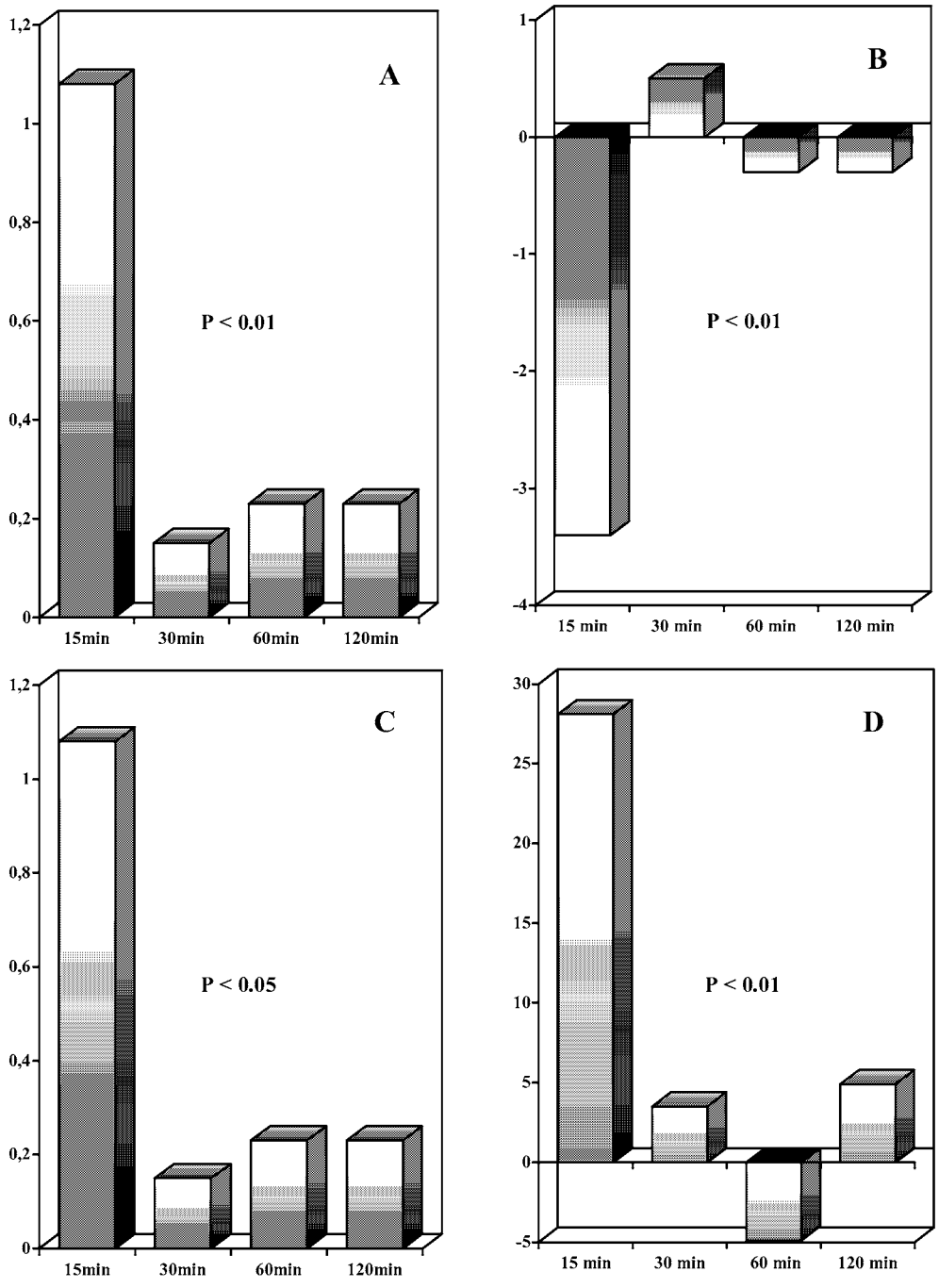
The criteria for the appearance of the warm-up phenomenon were predetermined as follows: the time to 0.1 mV ST-depression (STD) had to be lengthened by at least 1 min or the maximal ST-depression had to stay below the level of 0.1 mV during the second test. The number of patients demonstrating the phenomenon based on these criteria were 11/13 (85%), 4/13 (31%), 4/13 (31%) and 6/13 (46%) in the groups 1-4, in which the resting times between the two tests were 15, 30, 60 and 120 min, respectively (p=0.018).

6.12. Signs of ischemia, exercise tolerance and hemodynamics in repeated exercise testing (Study IV)

The primary end point was the time to 0.1 mV STD, which increased especially in group 1. Group 1 differed significantly from every other group also in post-hoc testing (p=0.025 for all comparisons to groups 2, 3 and 4). The computed variable ST/HR – slope represents developing ischemia with increasing heart rate, and the decrease in this slope during the second exercise test represents adaptation to ischemia. Although no significant changes in the maximal STD and the time required for the disappearance of ischemia (STD < 0.05 mV) were observed between groups, the total ischemic burden decreased in groups 1 and 4 during the second test, the decrease being most prominent in group 4. However, within the group the decrease in the maximal STD was significant in groups 1 and 3. The change in the time required for the anginal symptoms both to appear and to disappear was not significantly different between the groups. Neither was the change in the subjective degree of the symptoms. The differences in the ischemia parameters (exercise 2 – exercise 1) registered during exercise tests are presented in Figure 7.

At the time of the appearance of 0.1 mV STD the rate-pressure product during the second test was markedly higher in group 1 than in the other groups. The same held true also in post-hoc testing: $p < 0.05$ group 1 vs. 2, $p < 0.01$ group 1 vs. 3). The differences (exercise 2 – exercise 1) of the mean load of the last four minutes of exercise in the groups 1 – 4 were 6.0 ± 2.9, 5.2 ± 2.2, -4.1 ± 1.5 and –4.3 ± 4.4 W ($p < 0.05$). The differences of the calculated maximal oxygen consumption were 0.6 ± 0.4, 0.7 ± 0.3, -1.0 ± 0.3 and –0.8 ± 0.7 ml/min/kg, respectively ($p < 0.01$). Thus, the patients in the groups one and two exercised significantly better in the second test. The results from the differences for the maximal rate-pressure product demonstrated enhanced cardiac workload capacity during the second test in the first two groups ($p < 0.05$). This finding was explained mainly by a significant increase in the maximal heart rate during the second exercise ($p < 0.01$). The changes in blood pressure tended to act inversely compared to changes in heart rate and the means of the maximal blood pressure attained were lower in all four groups during the second exercise test.

Figure 7. Changes in ischemia parameters and cardiovascular exercise capacity between two successive exercise tests in randomly assigned groups of CAD patients with different resting periods. Δ = test 2–test 1.
A) Δ time to 0.1 mV STD (min). **B)** Δ ST/HR slope (μV/bpm). **C)** Δ ischemic burden (mV·min). **D)** Δ RPP at 0.1 mV STD (bpm·mmHg·100). Presented as mean values, P between groups.



6.13. Association of the angiographical degree of CAD and its risk factors and medication with warm-up phenomenon (Study IV)

The extent of the coronary artery disease was determined using a specific scoring system. The patients were divided into two groups according to the median value for the severity of the disease. The numbers of patients demonstrating warm-up phenomenon in those two groups were 17/26 (65%) and 8/26 (31%) (p=0.012), suggesting better ischemia adaptation in those with less extensive CAD. The existence of angiographically visible collaterals did not correlate with the appearance of the phenomenon.

Patients were divided into two groups on the basis of the median values for the LDL- and HDL-cholesterol. No significant differences in the ability for ischemia adaptation were observed between the groups. Furthermore, the existence of hypertension, smoking or use of antianginal medication did not explain the phenomenon.

6.14. HRV and HRT in patients with and without positive warm-up phenomenon (Study V)

Total power, ULF and VLF power and pNN50 calculated from the entire ECG recording were significantly higher in the group demonstrating warm-up phenomenon. In the assessment of the four short-term stationary phases (pre- and post-test 1 and 2) total power, VLF power and pNN50 were significantly higher in the warm-up positive group already at the baseline. In the analysis of repeated measures, HRV indices were decreased after the first exercise induced ischemia period in both groups approximately to the same level, the changes in total power, VLF and LF power and SDNN being significantly more prominent in the warm-up positive group. The recovery in HRV was attenuated in the warm-up negative group, although neither of the groups demonstrated total recovery to the baseline levels before the second exercise. The responses to the second exercise resembled those seen in the first test in both groups. Globally, the changes due to repeated exercise and consecutive episodes of ischemia tended to be attenuated in the group not demonstrating warm-up phenomenon. Furthermore, the overall behavior of LF power was significantly different between the groups throughout the whole test protocol. The behavior of total power and LF power are presented in Figure 9.

There were no significant differences between the groups in either TO or TS determined from the entire registrations. However, the number of VPCs tended to be lower and the number of different VPC morphologies was significantly lower in the warm-up positive group.

6.15. Relationship between HRV and the magnitude of ischemia adaptation (Study V)

In the warm-up positive group (n = 25) SDNN, total power, ULF power and VLF power determined from the entire recordings correlated with the change in IB in the recovery phase and also with the change in the total IB. Nonetheless, no significant correlation between HRV indices and the changes in other ischemia parameters was documented, however. Similarly, no significant correlation between HRV determined from the first 5-min baseline registration and changes in the ischemia parameters including IB was not shown. However, in the analyses of all four short-term stationary phases the change in the primary end point of all ischemia parameters, i.e. time to 0.1 mV ST-depression (test 1 – test 2), correlated positively with the changes in SDNN and RMSSD after the first exercise test (pre-test 1 – post-test 1) ($r = 0.42$ and $P < 0.05$ for both). The computed variable ST/HR-slope represents developing ischemia with increasing heart rate. The change in this slope (test 1 – test 2) correlated negatively with the change in HF-power after the first exercise test (pre-test 1 – post-test 1) ($r = -0.40$ and $P < 0.05$). These findings of dynamic changes in HRV suggest that in patients capable of ischemia adaptation, the magnitude of the phenomenon may well be related to the extent of disturbances in HRV induced by exercise and consecutive ischemia indicative of a less severe attenuation of HRV in the case of subjects exhibiting enhanced adaptation.

Figure 8. Changes in the characteristics of ischemia between two exercise tests. Left bars test one and right bars test two. Results are shown as mean ± SEM. P between groups for the delta values.

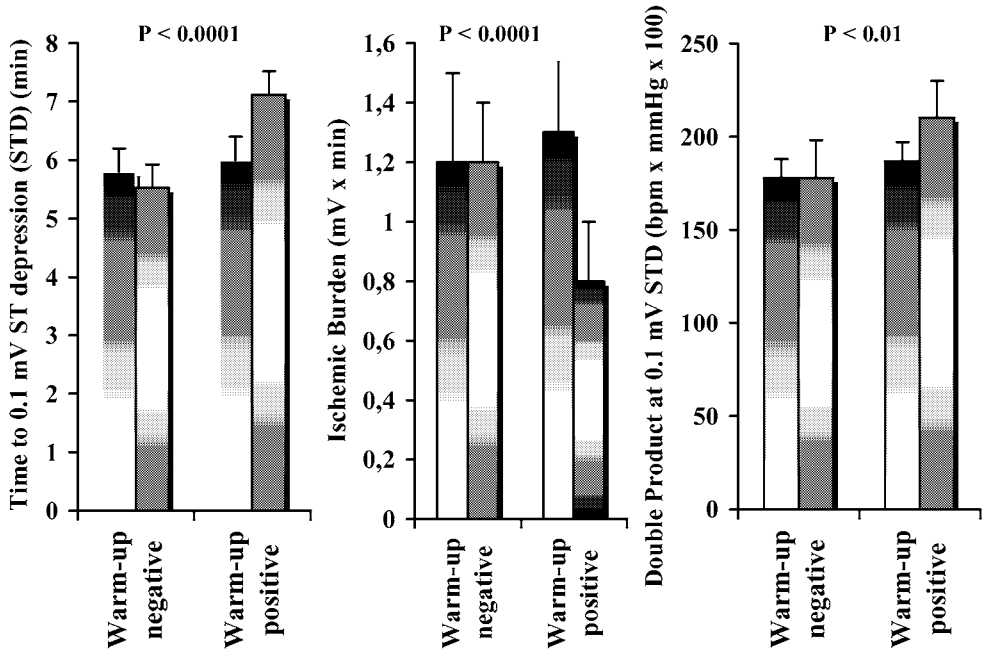
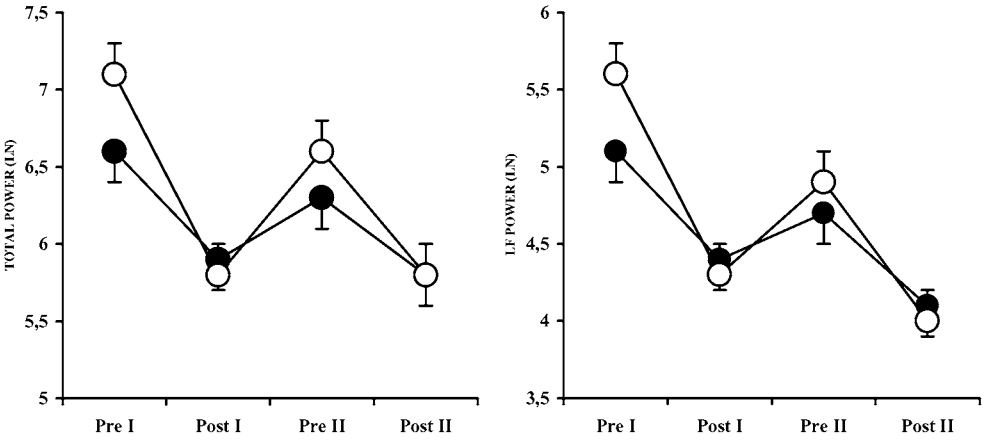


Figure 9. Changes in total power (left) and LF power (right) determined from stationary 5-min phases during the successive exercise test protocols in warm-up positive (open circles) and negative (closed circles) CAD patients. Results are shown as mean ± SEM.



7. DISCUSSION

7.1. Benefits of physical exercise in CAD and in sedentary population

The results of the present study showed that cardiorespiratory fitness is inversely related to the extent of carotid atherosclerosis, which in turn shows a good correlation with coronary atherosclerosis (Craven et al. 1990, Blankenhorn et al. 1993). Increased physical activity results in an increase in cardiorespiratory fitness, which is associated with decreased resting heart rate and increased heart rate variability. Two pioneering animal studies demonstrated the positive effect of decreased heart rate on the retardation of atherosclerosis (Kramsch et al. 1981, Beere et al. 1984). It is interesting to note that β-blockers, which are an essential component in CAD medication, lower heart rate and also increase heart rate variability especially by augmenting parasympathetic activity (Kamath & Fallen 1991, Cook et al. 1991, Schweizer et al 1993, Molgaard et al. 1993, Niemelä et al. 1994). In addition to being effective symptomatic drugs, they also can improve the prognosis in many CAD patients. The role of enhanced cardiac autonomic nervous function, which was related with improved cardiorespiratory fitness in middle aged men and with favourable warm-up phenomenon in CAD patients in the present series of studies, may well be of significant clinical relevance. Another mechanism, of course, could be the positive effect of exercise on the risk factors of atherosclerosis.

In the 6-year intervention, regular exercise of mild to moderate intensity was utilized. The improvement in cardiorespiratory fitness was evident, but the intensity of exercise may have been too low to evoke major differences in cardiac autonomic nervous function between the groups. However, in middle aged men, the most significant decrease in mortality has been observed between low and moderate levels of leisure time physical activity (i.e. exercise) but the mortality benefit was not markedly different when moderate and high levels of exercise were compared (Leon et al. 1987). In contrast, in one of the first studies, CVD risk was lower only if the physical activities included vigorous exercise (Morris et al. 1966). In a large trial in middle-aged men, where cardiorespiratory fitness was based on treadmill test performance and subjects were divided into five fitness groups, an increasing gradient in all-cause mortality was observed from the most to the least fit subjects. All-cause mortality was markedly reduced in the most fit group and also in the middle group compared to the least fit group (Blair et al. 1989). These findings suggest that at least moderate levels of physical

activity of moderate intensity are required to improve cardiorespiratory fitness together with life expectancy in middle aged men. Whether high intensity exercise supplies an additive positive effect or has even a negative influence on cardiovascular morbidity and mortality, remains unclear.

7.2. Physical activity and cardiorespiratory fitness in middle-aged men

In subjects with chronic cardiorespiratory or musculoskeletal diseases, the association between habitual physical activity and determined components of health-related fitness was more pronounced than in apparently healthy men. The observed relation was constant in the test-retest assessment with a 12-month interval. Thus, it could be interpreted that the relative contribution of regular physical activity in the preservation of cardiorespiratory fitness and in the control of body weight and adiposity as well as CAD risk factors may be more important in men with impaired health. Many previous trials have excluded subjects with chronic diseases and this may well have led to some underestimation of the favourable influences of regular exercise. However, in patients with CAD and peripheral occlusive artery disease, regular physical exercise has improved functional capacity as well as slowing the progression of the disease (Ernst & Matrai 1987, Hambrecht et al. 1993).

It could be hypothesized that men with serious health problems remember more precisely their daily routines including physical activity. In this group, cardiorespiratory fitness and body adiposity associated more strongly with energy expenditure, whereas the correlation between energy expenditure only at rest, i.e. a marker of physical inactivity, and fitness and fatness was similar in both groups. Globally, 7-day physical activity recall interview has appeared to produce highly reproducible results. The correlation between both determinations with a 12-month interval was only slightly lower than the observed correlation for measured maximal oxygen consumption and serum cholesterol level. These results support the observations from previous studies (Blair et al. 1985, Jacobs et al. 1993). Furthermore, use or self-administered questionnaires may result in overestimation rather than underestimation of performed physical activity compared to the more laborious interview as used in the present study.

7.3. Cardiorespiratory fitness and carotid IMT

One important original finding in the present study data is the inverse, graded association between cardiorespiratory fitness and carotid atherosclerosis. This cross-sectional observation has been recently confirmed in a controlled randomized 6-year exercise intervention trial, the DNASCO study (Rauramaa et al. 2004). The predilection sites for atherosclerosis are at the bifurcations and bends of the arteries, sites which from a pathophysiogical viewpoint are critical since there turbulent blood flow and low shear stress are combined (Glagov et al. 1988).

Long follow-up studies have reported an inverse relationship between a single measurement of cardiorespiratory fitness and mortality from atherosclerotic cardiovascular diseases years later (Ekelund et al. 1988, Blair et al. 1989, Sandvik et al. 1993, Laukkanen et al. 2004). It may even be considered as a reasonable surrogate end point for major cardiovascular events, since IMT of the carotid artery has also been shown to correlate directly with the extent and severity of coronary artery stenoses (Craven et al. 1990, Blankenhorn et al. 1993). Accordingly, we found that the subjects with exercise induced ischemic ST-segment changes in ergospirometry had higher carotid bifurcation IMT compared to subjects without marked changes in ECG.

The results of the present study support that proposal, since IMT was more than 60 % greater in the carotid bifurcation than in the distal common carotid artery in our middle-aged study cohort. Furthermore, due to the assumed lower prevalence of atherosclerosis in the common carotid artery, we found no relationship between VO2max and IMT of that particular determination site, while an inverse association between these parameters was evident in the bifurcation site. In our cohort, VO2max was 30 % greater in the highest vs. lowest quintile. This finding agrees with a previous study, which suggests that regular physical training may increase VO2max by a 30 % maximum in subjects aged $\geq$ 60 years (Seals et al. 1984). Increasing of blood HDL-cholesterol level is one acknowledged pathway of the observed antiatherosclerotic effect of regular exercise training (Moore 1994). We found a more powerful relationship between IMT and VO2max compared to IMT and HDL suggesting that enhanced cardiorespiratory fitness is an independent predictor of retarded progression of atherosclerosis in middle-aged men. While the association between cardiorespiratory fitness and carotid atherosclerosis was stronger in men with chronic diseases it must be noted that diagnosed cardiovascular disease may well have altered individual lifestyle

towards a healthier direction. That can partly be assumed from the observation that the dietary saturated fat intake was lower in the subjects with cardiovascular diseases. Moreover, emphasis should be put on our primary result, since the hypothesized interference of diagnosed cardiovascular disease with the relationship between carotid atherosclerosis and diet should theoretically be more prominent in subjects with chronic diseases.

7.4. HRV and HRT in the 6-year exercise intervention

The observed changes in HRV correlated significantly with the improvement in VAT during the six-year exercise intervention. During the intervention, VAT increased significantly in the exercise group and remained unchanged in the reference group. VO2max decreased in both groups, with the decrease being more prominent in the reference group. Interestingly, the proportions of subjects increasing their VAT were 74 % in the exercise group and 53 % in the reference group. The proportions of subjects increasing their VAT by more than 100 ml/min were 67 % and 38 % in both groups, respectively. This finding may be explained by the nature of the study design, where the reference group was not restrained in any way from doing physical activity. This was actually required by the local ethical committee. Therefore, the non-significant differences in the changes in HRV between the groups might well be due to this documented overlapping of changes in submaximal cardiorespiratory fitness. This explanation is supported by the observed significant correlation between the increase in VAT and the increase in HRV among all study subjects. Nevertheless, in middle-aged men, low to moderate intensity exercise training may not increase cardiorespiratory fitness enough to be able to cause marked differences in HRV between groups in this type of study design. Compared to a study on the mortality risk in post-MI patients (Kleiger et al. 1987) the means of SDNN were higher than 50 ms (dichotomizing point in the previous study) in both groups already at baseline. HF power is known to reflect vagal modulation of HR, but the physiological background of very low spectral components is somewhat unclear. We found a significant correlation to the change in VAT, especially in these frequency domain indices which have also been shown to predict mortality after MI (Bigger et al. 1992).

Like HRV, also HRT has been considered to reflect cardiovascular autonomic nervous regulation. Both TO and TS have been documented to correlate with SDNN in

ambulatory ECG registrations, but the findings have been somewhat controversial (Ghuran et al. 2002, Wichterle et al. 2002, Lindgren et al. 2003). In previous retrospective and prospective post-AMI studies, the following dichotomies were used in stratification of higher risk of events: TO $\geq$ 0 % and TS $\leq$ 2.5 ms/RRI (Schmidt et al. 1999, Ghuran et al. 2002, Barthel et al. 2003). Compared to these limits, the mean values of TO and TS were on the side of low risk already at baseline in both groups. Furthermore, no major changes between the groups were found during the intervention. Therefore, expectations that already somewhat normal values would markedly improve during the intervention may not be realistic. It may be more important to note that no decline in HRT was observed in this aging male population over six years. It has been reported that abnormal HRT is associated with advanced age, prior MI and left ventricular dysfunction in CAD, while TS has been found to correlate with age, but not with gender after AMI (Cygankiewicz et al. 2003, Jeron et al. 2003). Since there are no previous follow-up studies on HRT at the population level, the present study gains more importance as a pioneering follow-up involving also exercise intervention.

The results of the present study support previous reports and characterize more precisely the relationship between HRT and HRV. We found especially TS to correlate with most of the time and frequency domain variables and also with some of the nonlinear variables of HRV. Changes in HRT were observed over six years of intervention and those were associated with the changes in HRV, as might be assumed. In the Framingham Heart Study, low LF-power was the most potent predictor of mortality among all HRV variables in an elderly cohort. In comparison to those previous risk stratification studies in HRT and the Framingham study population, we found the most powerful correlation between the change in TS and the change in LF power (Tsuji et al. 1994, Schmidt et al 1999, Ghuran et al. 2002, Barthel et al. 2003).

In patients with CHF, physical training increases and the lack of exercise has decreased HRV and cardiac parasympathetic activity in some studies, but the results have been controversial (Adamopoulos et al. 1995, Kiilavuori et al. 1995, Duru et al 2000). Our study population consisted of a random sample of Eastern Finnish men in their late middle-age. Therefore, both healthy subjects and patients with previous cardiovascular disease were included in the trial. In the subjects of the present study, the most common cardiovascular diagnosis was hypertension and only a few had a diagnosed CAD or CHF. Previous results in this same study population showed that during a one-year training period, total and VLF power determined from short-term

ECG-registrations at supine rest increased in the exercise group and decreased in the reference group, while VAT increased by 11 % in the exercise group (Uusitalo et al. 2002). It is known that low to moderate intensity exercise training is suitable for rehabilitation of cardiac patients (Giannuzzi et al. 2003). Therefore, the effects of long-term exercise training on HRV and HRT might be more prominent in a selected patient group, e.g. CAD, where the baseline values would obviously be lower compared to the subjects of the present study. It has been suggested that baseline vagal tone may influence the individual training response (Hautala et al. 2003). In our study population, none of the HRV parameters at the baseline correlated significantly with the changes in the measured cardiorespiratory fitness.

The prognostic value of decreased HRV is evident in certain populations. Aging has been shown to reduce HRV both in ambulatory 24-hour ECG registrations and in short-term supine measurements. The reduction is affected by gender and in aging male population attenuation of HRV seems to be more global (Huikuri et al. 1996, Stein et al. 1997, Fukusaki et al. 2000). HRV might be reduced by up to 20 % during a 5-year follow-up period in healthy sedentary subjects (Agelink et al. 2001). In the Framingham Heart Study, decreased HRV was associated with a higher incidence of cardiac events during a mean follow-up of 3.5 years in subjects without clinical CAD or CHF (Tsuji et al. 1996). However, in that particular study less than half of the subjects were male. The results of the present study suggest that maintained and even improved submaximal cardiorespiratory fitness may be able to resist the detrimental effects of aging on HRV in middle-aged men. Whether increased HRV due to long-term low to moderate intensity exercise training lowers the risk of SCD and other cardiac events in middle-aged men, needs to be further studied in a larger study population. Furthermore, to investigate the effects of different doses of exercise on cardiorespiratory fitness and cardiac autonomic nervous function would require a different study design and also this issue remains to be further studied.

7.5. Expression and duration of warm-up phenomenon

The duration of endogenous protection induced by physical exercise has remained unclear. Warm-up phenomenon has been shown partially to disappear within 10 minutes to two hours in humans. In that previous study, there was a limited number of patients, it was not a randomized trial and antianginal medication was withdrawn 4 – 5 days

before the study and also patients with previous MI were excluded (Tomai et al. 1996). In another study, warm-up protection disappeared within 30 minutes. Also this trial had a small number of patients and only half of them underwent coronary angiography and thus had a definite diagnosis of CAD (Stewart et al. 1995). Furthermore, antianginal drugs were withdrawn two days before the study and not all patients underwent the entire study protocol. Our study was a randomized one recruiting a relatively large number of patients under antianginal medication and all patients underwent coronary angiography.

The results of the present study revealed that a considerable proportion of the CAD patients exhibited warm-up phenomenon, which does seem to disappear within a relatively short time. As in the case of ischemic preconditioning, there is no evidence for a second-window protection in the warm-up phenomenon. In the present study, the decrease in the ischemic burden during the second test was statistically significant only in the group with the shortest resting time (15 min) between the exercise tests, although the mean change tended to be even more prominent in the group with the longest resting time (120 min) between the tests. It is unclear if this points to reappearance of endogenous ischemia protection after two hours of rest. It has been suggested that peripheral mechanisms might be involved in the protection observed after two hours' rest (Tomai et al. 1996). However, in the present study, no evidence favouring peripheral vasodilatation as a factor for potential delayed protection was found. As previously demonstrated in animal models, the delayed protection seems to appear within 24 hours after the primary ischemic episode and finally to disappear within 96 hours (Baxter & Yellon 1997). The results of the present study have to be interpreted with caution, since to study the existence and time course of the second window protection would require a different timing of the repeated exercise tests.

Coronary vasodilatation and enhanced oxygen supply have been hypothesized to be the primary mechanisms of the warm-up phenomenon and a negative correlation between the degree of coronary artery stenoses and enhanced ischemia tolerance has also been observed (Jaffe & Quinn 1980, Tomai et al. 1996, Ylitalo et al. 1996a). In the present study, a special scoring system presented by Winkelmann et al. (1994) was used to quantify the extent of CAD. Those patients having less extensive disease demonstrated significantly better ischemia adaptation. This finding also favours coronary vasodilatation as the principal mechanism, especially when previous studies have shown an inverse relation between stenosis severity and vasodilatory capacity of

the affected coronaries (DiCarli et al. 1995, Ylitalo et al. 2001). The maximal rate-pressure product, the maximal oxygen consumption and the maximal ergometer workload attained were higher during the second test in groups one and two, demonstrating increased overall physical stress and probably also increased cardiac oxygen consumption, which is known to be correlated to the degree of coronary vasodilatation (Knabb et al. 1983, Uren et al. 1994). However, in group two, the ischemia adaptation was markedly less than that observed in group one, in spite of the increased rate-pressure product during the second test suggesting that other mechanisms in addition to coronary vasodilatation may also play a role. Interestingly, the degree of ischemia per se in the first exercise test (i.e. the power of the initial stimulus) measured by all of the ischemia parameters did not explain the degree of adaptation in the second exercise test.

7.6. Warm-up phenomenon and HRV

The present results suggest that CAD patients demonstrating adaptation to ischemia during repeated exercise have higher HRV compared to patients not capable of ischemia adaptation. Interestingly, the decrease in HRV caused by the first period of exercise induced ischemia appeared to be more prominent in warm-up positive patients. Although the values did not return to baseline levels before the second exercise test, the recovery of HRV also tended to be enhanced in the warm-up positive group. In conjunction with the observations concerning the behavior of LF-power, our results suggest that the tolerance of autonomic control might be wider in patients capable of ischemia adaptation. The magnitude of adaptation, measured by changes in ischemia parameters between the first and second test, correlated positively with overall HRV in patients demonstrating ischemia adaptation. Furthermore, better ischemia adaptation correlated with a less prominent attenuation in some of the HRV-parameters after the first exercise test. These findings suggest that there may also be some quantitative differences in cardiac autonomic nervous function and regulation in the CAD patients developing adaptation to ischemia.

Since the warm-up phenomenon is characterized with overall attenuation of signs of ischemia during repeated exercise, the phenomenon itself and the related better HRV and autonomic control could thus, at least in theory, be associated with a lower risk of malignant arrhythmias and sudden cardiac death during physical stress. In patients with

ischemia adaptation, VPCs have been shown to appear less frequently during repeated exercise and also during repeated vessel occlusion caused by coronary angioplasty (Airaksinen et al. 1995, 1999, Ylitalo et al. 1996b, 2001, Airaksinen & Huikuri 1997). The same seems to be true also in "real life", since the anti-arrhythmic effect has been confirmed in ambulatory ECG registrations (Pasceri et al. 1996). Interestingly, in our study, patients with ischemia adaptation had less multifocal VPCs than patients without adaptation, and there was also a tendency towards a smaller amount of VPCs in the adaptation group. It can be hypothesized that this, in conjunction with better HRV and cardiac autonomic control, could be beneficial also in the case of more severe ischemia e.g. the ischemia caused by abrupt coronary vessel occlusion and myocardial infarction.

It has been suggested that down-regulation of regional myocardial contractile function or alternatively coronary vasodilatation are the mechanisms in warm-up phenomenon (Jaffe & Quinn 1980, Okazaki et al. 1993, Tomai et al. 1996, Ylitalo et al. 2001). It has also been previously observed that warm-up phenomenon is associated with less severe CAD and vasodilatory capacity of the coronary arteries is associated with the severity of the stenoses (Knabb et al. 1983, Uren et al. 1994, Ylitalo et al. 1996). Autonomic regulation and parasympathetic modulation are involved in coronary vasodilatation, and reduced HRV may also be associated with the degree of CAD (Airaksinen et al. 1987, Rich et al. 1988, Hayano et al. 1990). We cannot be certain that it was improved vagal tone itself which would be associated with positive ischemia adaptation, though that could be assumed from the results of Tsuchiya et al. (1998). Their study revealed a positive relationship between increased preoperative HF-power and expression of IP during PCI. It is noteworthy that the protocol of ambulatory ECG registration of the present study differed from a normal routine 24-hour Holter recordings, e.g. containing two maximal stress tests and no sleeping hours, i.e. conditions not favoring periods of the appearance of maximal vagal tone even in theory. Interestingly, also position seems to play a role in heart rate variability and the low frequency component has been suggested to represent both sympathetic and parasympathetic activity in the upright position, while vagal activity is mainly involved in the supine position (Pomeranz et al. 1985, Pagani et al. 1986). It must be noted that in the present study the four short term registration periods were performed in the supine position and LF-power was the only HRV-parameter to show a significant group*time interaction between the groups throughout the whole test protocol. It can be hypothesized that if the vagal component really plays a role, increased coronary flow

and perhaps additive decreased myocardial oxygen consumption form a link to IP and warm-up phenomenon. Thus it remains unclear, whether better cardiac autonomic control is a primary determinant of warm-up phenomenon or vice versa.

Decreased HRV is a strong and indepedent predictor of mortality after MI (Wolf et al. 1978, Kleiger et al. 1987, Farrell et al. 1991, Bigger et al. 1992), and in the Framingham study poor HRV has also been documented to be related to a high incidence of new cardiac events (Tsuji et al. 1996). In an elderly cohort of the Framingham Heart Study, low LF-power, as determined from ambulatory ECG registrations lasting only one to two hours, was the most potent predictor of mortality among all HRV variables (Tsuji et al. 1994). Accordingly, in our analysis of four stationary phases the only HRV-variable to present significant group*time interaction throughout the whole protocol was LF-power. Therefore, changes in autonomic nervous function during exercise induced ischemia may be of clear clinical significance in CAD. One target of interest in future research will be to investigate the relationship between warm-up phenomenon including autonomic control and both morbidity and mortality in CAD patients.

8. CONCLUSIONS

Physical activity associates beneficially to cardiorespiratory fitness, body fatness and traditional CAD risk factors, essential components of health-related fitness, in middle-aged men with chronic diseases. Low cardiorespiratory fitness is an independent predictor of carotid atherosclerosis. Furthermore, improved submaximal cardiorespiratory fitness associates with favorable changes in HRV, acting to oppose the effects of normal aging in middle-aged men. Importantly, low to moderate intensity exercise training has beneficial effects on cardiac autonomic nervous regulation, an important predictor of fatal and nonfatal cardiac events. Regular physical exercise plays an important role in preserving and improving cardiovascular health.

Many of the patients with diagnosed CAD are able to recruit endogenous protective mechanisms during repeated physical exercise and consecutive ischemia, i.e. they exhibit warm-up phenomenon. However, this protection seems to disappear within a relatively short time. Adaptation to myocardial ischemia is markedly better in patients with less extensive CAD suggesting that coronary vasodilatation probably plays the main role, but other mechanisms may also be involved. Furthermore, cardiac autonomic regulation seems to be better preserved in CAD patients capable of ischemia adaptation and the magnitude of adaptation may be related with the changes in autonomic tone.

The true prognostic significance of warm-up phenomenon and related autonomic control as well as the existence of real delayed or second window protection will require further research. Whether regular physical exercise below the ischemic threshold is able to enhance expression of warm-up phenomenon in CAD, also remains to be investigated. At the population level the dose-dependent effects of regular exercise training must also be studied to permit adequate and more individual prescription of exercise in both primary and secondary prevention of cardiovascular disorders.

9. FUTURE INVESTIGATIONS

There are important targets to study in future investigations. It would be useful to conduct a long-term controlled, randomized trial to evaluate the effects of regular physical exercise training on warm-up phenomenon and its role in the prognosis of CAD in angiographically confirmed patients. Furthermore, dose-dependent effects of long-term regular exercise on cardiac autonomic control and carotid atherosclerosis (primary prevention) in a sedentary middle-aged population could be a target for further examination. Finally, the existence, time-course and clinical determinants of the second window protection in warm-up phenomenon all require further clarification.

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