Exercise Testing in the Prediction of Cardiovascular Diseases and Mortality

A Prospective Population Study in Men

Doctoral dissertation

To be presented by permission of the Faculty of Medicine of the University of Kuopio for public examination in Auditorium, Mediteknia building, University of Kuopio, on Saturday 10th December 2005, at 12 noon

Research Institute of Public Health
University of Kuopio
Kuopio Research Institute of Exercise Medicine
Both treadmill and cycle exercise tests are widely accepted diagnostic testing methods with their typical advantages. In previous studies, physical fitness has been one of the strongest risk factors for cardiovascular diseases (CVDs). Both exercise-induced painful and painless ischemia have been previously documented as risk predictors for ischemic cardiac events. Systolic blood pressure during exercise test is an important hemodynamic variable. However, the prognostic value of systolic blood pressure during recovery from exercise is not largely known with respect to acute myocardial infarction.

Cardiorespiratory fitness, exercise-induced myocardial ischemia and systolic blood pressure were assessed using a maximal, symptom-limited exercise test on an electrically braked cycle ergometer. Respiratory-gas exchange was measured for 2361 men in a population based sample of men. During the follow-up, the classification of acute coronary events was carried out according to the multinational MONICA project protocol, and deaths were ascertained by linkage to the National Death Registry. One metabolic equivalent increment in maximal oxygen uptake (3.5 kg/mL.min in minute) was related to a decreased risk of coronary heart disease (CHD) death in both healthy (relative risk 0.8, 95 % confidence intervals, CI 0.7 to 1.0) and unhealthy (relative risk 0.7, 95 % CI 0.6 to 0.8) men after adjustment for age, cardiovascular risk factors, exercise-induced myocardial ischemia and maximal heart rate. Men with silent ischemia during exercise had a 1.7-fold (95 % CI 1.1 to 2.6) risk of acute coronary events and a 3.5-fold (95 % CI 1.9 to 6.5) risk of CHD death compared with men without silent ischemia after adjusting for risk factors. Silent ischemia during exercise had a stronger association with the risk of acute coronary events and CHD death in smokers, in hypercholesterolemic men and in hypertensive men than in men without such risk factors. Systolic blood pressure of over 195 mmHg at two minutes recovery was related to a 1.7-fold (95 % CI 1.2 to 2.3) risk of acute myocardial infarction, and men with the largest difference in systolic blood pressure from rest to recovery (over 64 mmHg) had a 1.4-fold (95 % CI 1.1 to 1.8) risk of acute myocardial infarction compared to men with the smallest difference in systolic blood pressure.

Exercise capacity provides a valuable tool for the prognostic assessment of CVD risk. Cardiorespiratory fitness provides additional prognostic information with the presence of other risk factors, and can be considered at least as important a risk factor as smoking, poor lipid profile, hypertension, type 2 diabetes and obesity. Silent myocardial ischemia during exercise testing predicts acute coronary events and CHD death in men clinically free of CHD. The clinical implication of this study is that painless myocardial ischemia is of significant additional prognostic value when any conventional risk factors are present. The present findings emphasize the importance of exercise testing in identifying high risk persons who are in the greatest need of preventive measures. Systolic blood pressure responses during recovery from an exercise test can be used as an additional risk marker for identifying individuals at an increased risk for acute myocardial infarction.


Yeinen suomalainen asiakasaste: epidemiologia; sydän- ja verisuonitaudit; riskitekijät; fyysinen kunto; sydäninfarkti; verenpaine; miehet; Suomi
Dedicated to my late father
ACKNOWLEDGEMENTS

This study was carried out at the Research Institute of Public Health, University of Kuopio, Kuopio, Finland, and Kuopio Research Institute of Exercise Medicine, Kuopio, Finland.

I wish to thank my principal supervisor, professor Timo A. Lakka, M.D., Ph.D., for his valuable comments and support during my Ph.D. work. His knowledge of epidemiological and clinical research has been very important during my Ph.D. work.

I am indebted to my supervisor, professor Jukka T. Salonen, M.D., Ph.D., M.Sc. P.H., for the opportunity to do my Ph.D. work at the Research Institute of Public Health and for his support during my research work. His knowledge in cardiovascular epidemiology has been of great importance.

I am thankful to professor Rainer Rauramaa, M.D., Ph.D., M.Sc. for his valuable support during my Ph.D. work at the Kuopio Research Institute of Exercise Medicine. His skills in evidence-based exercise medicine have been very helpful.

I thank my principal co-worker Sudhir Kurl, M.D., for his valuable advices and excellent support throughout this study.

I am deeply grateful to all other people who have contributed this work. I wish to thank:

Professor Arthur S. Leon, M.D., Ph.D. and professor Robert Fagard, M.D., Ph.D., for their excellent professional work in reviewing my thesis.

Co-authors Juha Venäläinen, M.D., Riitta Salonen, M.D., Ph.D., Raimo Kuhanan, M.Sc., Jaakko Eränen, M.D. and Tomi-Pekka Tuomainen, M.D., for their valuable contribution to this work.

Raimo Kettunen, M.D., Ph.D. and Matti Huttunen, M.D., for valuable comments on the role of scientific work in bedside cardiology.

Professor Jussi Kauhanen, M.D., Ph.D., professor Leo Niskanen, M.D., Ph.D., docent Kristiina Nyyssönen, Ph.D., docent Sari Voutilainen, Ph.D., docent Jari Kaikkonen, Ph.D., Pertti Happonen, M.D., Hanna-Maaria Lakka, M.D., Ph.D., Kai Savonen, M.Sc., Veli-Pekka Valkonen, M.D., Tiina Rissanen, Ph.D., Jaakko Mursu, M.Sc., Jyrki Virtanen, Ph.D., and Tarja Nurmi, Ph.D., for friendship and interesting scientific discussions.

Kimmo Ronkainen, for his help in statistical analysis and Sonja Rissanen, for helping in office work.
Tuula Tiihonen, Hannele Kastarinen, Tuula Turunen and Merja Turunen for data collection in the study.

Esko Taskinen, M.D., Hannu Litmanen, M.D. and Arno Heikelä, M.D., for supervising a part of the exercise tests.

I express my warmest thank to the Department of Internal Medicine, Savonlinna Central Hospital, Savonlinna, Finland.

This study was supported by the Academy of Finland, the Ministry of Education of Finland, City of Kuopio, Juho Vainio Foundation, Maud Kuistila Foundation, Finnish Cultural Foundation of Northern Savo, Finnish Medical Foundation, the Finnish Foundation for Cardiovascular Research and the Foundation for Research in Health, Exercise and Nutrition.

This thesis is dedicated to my late father and my lovely mother. Finally, I want to thank Tanja, Henri and Sanjtu for their loving support. Their continued unfailing patience and understanding has been most valuable and unforgettable part in my life.

December 2005

Jari Laukkanen
### ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>CHD</td>
<td>Coronary heart disease</td>
</tr>
<tr>
<td>CVD</td>
<td>Cardiovascular disease</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>HDL</td>
<td>High density lipoprotein</td>
</tr>
<tr>
<td>ICD</td>
<td>International Classification of Diseases</td>
</tr>
<tr>
<td>KIHD</td>
<td>Kuopio Ischemic Heart Disease Risk Factor Study</td>
</tr>
<tr>
<td>LDL</td>
<td>Low density lipoprotein</td>
</tr>
<tr>
<td>L</td>
<td>Liter</td>
</tr>
<tr>
<td>MET</td>
<td>Metabolic equivalent</td>
</tr>
<tr>
<td>MONICA</td>
<td>MONItoring of Trends and Determinants in CArdiovascular Disease</td>
</tr>
<tr>
<td>RR</td>
<td>Relative risk</td>
</tr>
<tr>
<td>VO₂max</td>
<td>Maximal oxygen uptake</td>
</tr>
</tbody>
</table>
LIST OF ORIGINAL PUBLICATIONS

This dissertation is based on the following original publications:


5. RESULTS
5.1 Baseline characteristics 51
5.2 Exercise test findings 53
5.3 Cardiorespiratory fitness and mortality 54
  5.3.1 Cardiorespiratory fitness and mortality among men
  without previous cardiovascular disease 54
  5.3.2 Cardiorespiratory fitness, cardiovascular risk factors,
  all-cause and cardiovascular mortality 56
5.4 Exercise-induced silent myocardial ischemia, coronary morbidity
  and mortality 58
  5.4.1 Silent myocardial ischemia at baseline and outcomes 58
  5.4.2 Silent myocardial ischemia and the risk of acute
  coronary events and coronary heart disease death 58
  5.4.3 Silent myocardial ischemia, other risk factors and the risk
  of cardiovascular events 59
5.5 Systolic blood pressure during recovery from exercise and the risk
  of cardiovascular events 61
  5.5.1 Systolic blood pressure at rest, during and after exercise 61
  5.5.2 Systolic blood pressure during recovery and
  acute myocardial infarction 61
  5.5.3 The difference in systolic blood pressure from rest to
  recovery and acute myocardial infarction 62
  5.5.4 Systolic blood pressure during recovery and
  cardiovascular mortality 63

6. DISCUSSION 64
6.1 Methodological aspects 64
  6.1.1 Epidemiologic study 64
  6.1.2 Study population 65
  6.1.3 Exercise testing 65
  6.1.4 The prognostic and diagnostic use of exercise test 67
  6.1.5 Collection and classification of cardiovascular events 68
6.2 Cardiorespiratory fitness and cardiovascular mortality 69
6.3 Silent myocardial ischemia and the risk of coronary heart disease 72
6.4 Systolic blood pressure during recovery from exercise and
  the risk of coronary heart disease 75

7. SUMMARY AND CONCLUSIONS 78
  1. implication
  2. implication
  3. implication
  4. implication

8. REFERENCES 79

9. ORIGINAL PUBLICATIONS
1. INTRODUCTION

Cardiovascular diseases (CVDs) are the leading cause of death in Western countries, however, many patients with prognostically significant coronary artery disease are asymptomatic (1). Exercise testing has been used in everyday clinical practice for a long time, and it has contributed significantly to the diagnostics of coronary heart disease (CHD) and the management of patients with CVD or at a high risk for CVD. Exercise test combined with electrocardiogram (ECG) is primarily used for the detection of ST wave changes secondary to myocardial ischemia. Although other clinical findings, such as dyspnea on exertion, resting ECG abnormalities, or multiple risk factors for atherosclerosis, may suggest the possibility of CHD, the most predictive clinical finding is a history of chest pain or discomfort.

Clinical exercise testing consists of the continuous monitoring of an ECG with frequent recordings. Regular blood pressure and heart rate recordings are made before, during, and after exercise test on treadmill or cycle ergometer with progressively increasing exercise intensity. Low cardiorespiratory fitness, ischemic ECG findings and abnormal blood pressure responses during exercise testing are known to be related to an increased incidence of CHD. Previously the main focus has been on ECG recordings and chest pain during exercise test for screening CHD. Modern exercise testing, however, is not only limited to observation of ischemic ECG findings during exercise. More information can be derived from exercise capacity, heart rate and blood pressure responses and the development of arrhythmias during exercise test as well as heart rate and blood pressure responses and ECG changes during recovery period. In recent years, increasing amount of attention has been directed toward using exercise testing to measure therapeutic responses to lifestyle changes or pharmaceutical and invasive interventions.

Global risk assessment, including exercise testing, is useful for assessing relative risk and absolute long-term risk in middle-aged individuals. Even though short-term risk may not be high in individuals who have conventional risk factors, long-term risk can be high. This highlights the need for early and prolonged intervention on cardiovascular risk factors. Although long-term prevention may not always call for the use of risk-reducing drugs, it
definitely requires the introduction of lifestyle modification including smoking cessation, increased physical activity, a low fat and high fiber diet and weight control. Besides the assessments of conventional risk factors, many parameters recorded during exercise testing help the global risk stratification.

There is a need for easily available noninvasive methods to define individuals with an increased risk of atherosclerotic CVDs and the greatest need for preventive measures. The main aim of the current study is to identify useful predictors for CVD and mortality during exercise testing that would provide additional prognostic value to conventional risk factors in a population based sample of men.
2. REVIEW OF LITERATURE

2.1 Exercise testing in risk prediction

Risk factor assessment determines the therapeutic strategy, because the intensity of preventive intervention is tailored to the patient’s risk of CHD (2). The most important risk factors for CHD include high age, elevated serum total cholesterol and low-density lipoprotein (LDL) cholesterol, low high-density lipoprotein (HDL) cholesterol, elevated blood pressure, cigarette smoking, diabetes, obesity, physical inactivity, family history of CHD and menopausal status in women. Aggressive risk factor reduction, formerly used in secondary prevention, may be pivotal to optimal patient management in primary prevention (2, 3). In addition to exercise training, a comprehensive secondary prevention program for patients with CHD requires aggressive reduction of risk factors through nutritional counselling, weight management, and adherence to prescribed drug therapy (4, 5).

Noninvasive testing modalities have the potential to measure and monitor atherosclerosis in asymptomatic high-risk subjects (5). Noninvasive methods such as exercise testing may be more appropriate than invasive approaches to select high-risk persons for therapy. Exercise ECG has been widely used as an important noninvasive testing method in a clinical practise.

Myocardial ischemia is considered the most important cause of chest pain and is a consequence of underlying CHD. However, sometimes CHD may be without symptoms due to a preclinical stage of the disease, collateral formation or extensive medical therapy as well as individual’s differences in pain threshold (6). Non-obstructive coronary artery disease that has not resulted in sufficient luminal occlusion to cause ischemia during exercise can still lead to ischemic events through spasm, plaque rupture, and thrombosis, but most dangerous events are usually associated with extensive atherosclerosis. These non-critical lesions in coronary arteries explain some of the events that occur among individuals with a slightly abnormal changes or even normal findings in exercise test (6-8).

Exercise testing combined with ECG was used primarily for the detection of ST changes secondary to myocardial ischemia. Exercise testing is typically used if the diagnosis of
CHD is uncertain. However, ischemic ST changes in exercise ECG have been considered to lack both sensitivity and specificity in order to make them applicable for detecting asymptomatic subjects at increased risk of death. Although many clinicians rely almost solely on their interpretations of the exercise test on ECG changes, ST-segment depression alone does not always provide adequate prognostic information (9).

Additional factors that may improve the value of exercise testing include hemodynamic and chronotropic responses. Important information may be derived from exercise capacity, heart rate and blood pressure responses, development of arrhythmias, and whether or not symptoms such as chest pain develop during exercise (10). This allows the assessment of the presence and severity of ischemia, prognosis, overall functional capacity, and the efficacy of therapeutic interventions. Although exercise testing in cardiological evaluation can be combined with radionuclide or echocardiographic imaging, ECG, blood pressure and heart rate responses and exercise capacity remain the main measures used in clinical practise (10).

2.2 Exercise testing protocols

2.2.1 Cycle exercise test

Electrically braked cycles vary the resistance to the pedaling speed permitting good control of power output. The highest values of maximal oxygen uptake \( \text{VO}_{2\text{max}} \) and heart rate are obtained with pedaling speeds of 50 to 80 rpm, and therefore are the most often recommendable speeds (7). Exercise test on a cycle ergometer is non-weight bearing and can be used in individuals who are accustomed with cycling although they may have difficulties in walking and running. A major limitation of cycle ergometer testing is the fatigue of the quadriceps muscles. Power output control is difficult for subjects who are fatigued or unable to co-operate using required pedaling speed. Leg fatigue may cause an inexperienced subject to stop before reaching a true \( \text{VO}_{2\text{max}} \). It is observed that \( \text{VO}_{2\text{max}} \) is generally 10% to 15% lower in a cycle test than in a treadmill test among individuals who are not accustomed to cycling (7, 11, 12). Cycle ergometers are generally less expensive, smaller, safer and less noisy than treadmills, and cycle ergometer produces less motion of
the upper body.

Protocols for clinical exercise testing include an initial warm-up with low workload, progressive uninterrupted exercise with increasing workloads and an adequate time interval in each level of exercise. During the various stages of cycle exercise including recovery period, many exercise test parameters can be measured. The initial power output is usually 10 to 20 W, followed by increases of 20 to 25 W every 1 to 3 minutes until end point or maximal exercise capacity are reached. In many studies in Europe, 20 W increments per 1 minute are typically used during cycle exercise (7). If arm ergometry is substituted for cycle ergometry, a similar protocol may be used, except that initial power output and incremental increases are lower (7, 13).

2.2.2 Treadmill exercise test
The treadmills have the possibility to change speed and grade. Several different treadmill protocols are defined according to treadmill speed, grade, and stage duration. When aerobic capacity is to be estimated from exercise time or peak workload, protocols with large stage-to-stage increments in energy requirements should be avoided because of their weaker relationship between oxygen uptake and workload (13-15). The limitation is that the use of handrails for support reduces the workload being performed. However, subjects should be encouraged not to tightly grasp the front or side rails because this action supports body weight and reduces the workload.

The Bruce multistage maximal treadmill protocol has 3-minute periods to allow achievement of a steady state before workload is increased (7). A limitation of Bruce protocol is relatively large increase in workload that can make estimation of VO2max and hemodynamic responses more difficult. Some subjects are forced to stop exercising prematurely because of an inability to tolerate the high workload increments. The advantage of this protocol is the value of 3-minute stages to acquire submaximal data from exercise. Initial zero or one-half stages (1.7 miles per hour at 0% and 5% grades) can be used for subjects with compromised exercise capacities. The Balke and Naughton protocols keep the speed constant and only modestly increase treadmill elevation at each stage are preferable for this purpose (16, 17). Protocols with 1 to 2 minute stages with 1 metabolic
equivalent (MET) increment between stages are more suitable for patients with limited exercise tolerance. Functional capacity can also be accurately determined using ramp protocols with small increments in work rate per stage. Ramp protocols are started at a relatively low treadmill speed, which is gradually increased. The ramp angle of incline or workload is progressively increased at fixed intervals (i.e. 10 to 60 seconds) starting at 0 grade, with the increase in grade calculated on the patients estimated functional capacity such that the protocol will be completed in 6 to 12 minutes. In this type of protocol, the rate of work increases continuously, and steady states are not easily reached. A limitation of ramp protocols is the requirement to estimate functional capacity from an initial cardiorespiratory fitness scale and adjust the ramp accordingly. Thus, it is important that ramp exercise protocols should be individualized according to the initial cardiorespiratory fitness level (15).

2.3 Cardiorespiratory fitness

2.3.1 Indirect assessment of cardiorespiratory fitness
Regardless of the specific protocol chosen, the protocol should be tailored to the individual to yield a fatigue-limited exercise duration of about 10 minutes (14, 15). Shorter durations may produce a nonlinear relationship between oxygen uptake and workload and a higher anaerobic rate of metabolisms during exercise test, whereas durations over 15 minutes may cause most subjects to terminate exercise because of inadequate aerobic endurance capacity (17). The optimal duration for an exercise protocol is 6 to 12 minutes and should be adjusted to the subject’s needs. In general, 6 to 12 minutes of continuous progressive exercise during which the myocardial oxygen demand is elevated to the subjects’ maximal level is optimal for both diagnostic and prognostic purpose.

Exercise capacity can be measured indirectly by estimating VO2max from the highest treadmill or cycle workload achieved. Maximal work capacity in normal individuals is influenced by familiarization with the type of exercise test and the level of exercise training. The simple 6-minute walking test, that measures the distance walked on level ground in 6 minutes, can be used as a prognostic test among patients with congestive heart
failure, marked left ventricle dysfunction or peripheral arterial occlusive disease and among those who cannot perform cycle or treadmill exercise due to low initial exercise capacity (18). The 6-minute walking test is moderately predictive of VO$_{2max}$ in patients with advanced heart failure (19).

Indirectly measured exercise capacity should be reported in estimated peak METs of exercise as an index measure of exercise capacity (7, 8). The MET is the ratio of the metabolic rate during exercise to the metabolic rate at rest. One MET is defined as the oxygen uptake when a person is at rest, which is equivalent to 3.5 mL of oxygen consumption per kilogram of body weight per minute. The use of this measure has the advantage of providing a common assessment of cardiorespiratory fitness for use with various exercise protocols (7). When exercise capacity is reported as the duration of exercise test, the nature of the exercise test protocol should be clearly specified because the exercise time depends on the protocol. Serial comparison of exercise capacity in individual patients to assess significant interval change requires a careful examination of the exercise protocol used, cardioactive drug therapy and other conditions that might influence test performance.

### 2.3.2 Direct assessment of cardiorespiratory fitness

The direct measurement of VO$_{2max}$ is a gold standard for assessing the amount of the oxygen consumption in maximal effort (7, 8). It is the most reliable and reproducible methods for the assessment of functional capacity (7, 20). VO$_{2max}$ is the greatest amount of oxygen a person can take in from inspired air while performing dynamic exercise. A plateau of oxygen consumption can be reached at the workload after which any further power increase occurs without increase in oxygen uptake. VO$_{2max}$ is measured in litres of oxygen consumed per minute using respiratory gas analysis. METs can be obtained by dividing VO$_{2max}$ in millilitres per minute by the product of body weight (kg) x 3.5. Exercise protocols with large increments in work rate per stage limit the reliability of both direct and indirect measures of VO$_{2max}$ (14). Gas exchange data with the assessment of heart rate, blood pressure and ECG can provide important information to evaluate functional capacity and even distinguish cardiovascular from pulmonary limitations during exercise (8).
2.3.3 Determinants of cardiorespiratory fitness

$V_{O_2}^{\max}$ during exercise represents cardiac, circulatory and respiratory function and muscle oxygen utilization under physiological stress conditions. $V_{O_2}^{\max}$ which is a product of cardiac output and maximal arteriovenous oxygen difference is determined by age, gender, the duration, intensity, frequency and type of physical activity, genetic factors and clinical or subclinical disease (7). Age, gender and underlying diseases are determinants of initial cardiorespiratory fitness level, although they are not major determinants of responses to regular physical activity. However, the pre-training level of a phenotype may contribute to the variability in training response in some individuals (21-23). Therefore, the level of physical activity sufficient to improve or maintain $V_{O_2}^{\max}$ probably depends on the initial health and cardiorespiratory fitness status, the length of training history and the duration, frequency and intensity of exercise.

Cardiorespiratory fitness is a physiological measure that can be considered as a marker for the participation of physical exercise. Cardiorespiratory fitness is a component of physical fitness defined as the ability of the cardiovascular and respiratory systems to supply oxygen to the working muscles during dynamic exercise. Aerobic fitness reflects the maximal functional capacity of the integrated performance of the heart, lungs, vascular system, and muscle tissue, and is a measure of the maximum aerobic exercise which can be sustained while aerobic replenishment of muscle high energy phosphates can occur. Cardiorespiratory fitness stands in the similar type of relationship to physical exercise as blood cholesterol levels to diet rich in fat, although some authors have included physical exercise and physical fitness into one category (24). Physical fitness is a marker of biological capacity and has suggested to include (I) the ability of the circulatory and respiratory systems to supply fuel during physical exercise and to eliminate fatigue products, and (II) body composition including the relative amounts of muscle, fat and bone of the body (7).

Although physical activity may be an appropriate therapy for the unfit subjects, inactivity is not the only cause of being unfit when subclinical disease or genetics are involved (21, 24). As $V_{O_2}^{\max}$ is used as a measure of cardiorespiratory fitness, it is important to understand the relative contributions of genetic endowment and environmental influences.
in its determination. The genetic contribution is more modest being of the same order as the heredity contribution to blood cholesterol levels (22, 25).

2.4 Heart rate response during exercise

During the exercise test, the heart rate rise proportionately with the intensity of the workload. Excessively rapid rises in heart rate result primarily from reduced left ventricular function and stroke volume, which, in turn, may be caused by physical deconditioning or cardiac disease. Under such circumstances, the heart rate reaches its peak value at low level of exercise that limits maximal exercise capacity. When the heart rate response to exercise is excessively attenuated in the absence of rate-limiting drugs, this condition is termed chronotropic incompetence. It has been reported that low heart rate response to exercise is a risk predictor for sudden cardiac death (26).

In addition, heart rate can be used as an estimate of oxygen consumption. However, the limitation of this measure is that there is non-linear relationship between oxygen uptake and heart rate. The nonlinearity tends to be greatest at the top and bottom ends of VO$_2$/heart rate plots, heart rate being lower than suggested by a linear relationship at low VO$_2$ values and higher at near maximum levels of VO$_2$ (7).

An abnormally high heart rate during submaximal workloads as well as during recovery could be due to deconditioning, anemia, metabolic disorders, or any other condition that decreases vascular volume or peripheral resistance. This finding is relatively frequent soon after myocardial infarction and in CHD. Submaximal heart rate may be lower due to exercise training, enhanced stroke volume and peripheral oxygen utilization or drugs. The use of β-blockers, which lower heart rate, limits the interpretation of the heart rate response to exercise. Furthermore, conditions that affect the sinus node can attenuate the normal response of heart rate during exercise testing. Abnormal heart rate during recovery period refers to relatively slow deceleration of heart rate following exercise cessation. This type of response reflects decreased vagal tone and high heart rate recovery is associated with increased mortality (27). It is suggested that when the postexercise phase includes upright cool down, a decrement in heart rate of 12 beats per minute or less is abnormal (28).
2.5 Myocardial ischemia during exercise

The noninvasive diagnostic tests such as ECG are used to detect myocardial ischemia associated with obstructive CHD. To date, their greatest application has been diagnostic, in the evaluation of patients with symptoms of angina or a previous clinical manifestation of CHD. One limitation of the methods used to detect exercise-induced myocardial ischemia is the dependence of these methods on the presence of flow-limiting coronary stenosis. By exercise testing with ischemic ECG findings can be found angiographically demonstrable CHD, which is usually defined as greater than 50 % stenosis of major coronary arteries (29). The traditional reference standard against which the exercise ECG has been measured is a qualitative assessment of the coronary angiogram using 50 to 70 % obstruction of the lumbar diameter as the angiographic cutpoint.

The predictive value of exercise ECG is dependent on the prevalence of disease in the population tested. When used in a population with a low prevalence of CHD, such as an asymptomatic population including middle-aged subjects undergoing cardiovascular screening, these tests are expected to have low positive predictive value, and the majority of positive test results represent false-positive responses (3). In a high risk population, such as those aged over 50 with typical angina symptoms, a negative result cannot always rule out CHD, though the results provide more prognostic information (30). The yield of screening individuals with exercise testing has been greater in higher risk groups (29). Morise et al (31) found that the sensitivity and specificity were significantly greater in men than in women. Some previous findings suggest that exercise-induced ST depression can better predict high risk in patients after acute myocardial infarction (32).

Conclusions drawn from exercise tests are generally based on patients with chest pain or discomfort, with only certain patients being selected for further evaluation in normal clinical practise (33). Because of good clinical practise, only a portion of subjects with chest pain or dyspnea undergo exercise testing and finally cardiac catheterization (33, 34). Cardiac catheterization would be chosen particularly for those with a low exercise capacity and abnormal ST-segment response. This is due to the selection that the low risk patients who are excluded from cardiac catheterization after the exercise test will be those with a
high exercise capacity and a normal ST-segment response (34). It is also proposed that the magnitude of ST depression on symptom-limited exercise testing does not correlate with the extent of ischemic myocardium, and the amount of ST depression at maximal workload resolving quickly after exercise may not indicate the severity of CHD (35). However, early-onset and deep ischemic ST changes with low exercise capacity are related to more severe CHD and poor prognosis. From the clinical point of view, it should be recognized that an abnormal exercise ECG finding cannot identify asymptomatic subjects destined to develop abrupt changes in plaque morphology.

The coronary circulation supplies the heart with oxygen and nutrients to maintain cardiac function, and thus supply the remainder of the body with blood. Myocardial oxygen demand has been indexed by the product of systolic aortic pressure and systolic duration, whereas myocardial oxygen supply can be indexed by the product of diastolic time and mean diastolic pressure. Coronary angiography provides most reliable anatomical information for determining the appropriateness of medical therapy, percutaneous coronary intervention or coronary artery bypass grafting. The limitation of angiography to determine the functional significance of coronary stenosis can overcome by measurements of coronary circulation and blood flow. The hemodynamic and physiological significance of a given stenosis cannot be measured always by using angiography, and thus, the effect of the angiographic estimates of coronary narrowing on coronary flow and myocardial metabolism is not clear. On the other hand, exercise testing can provide useful additional information about the degree of functional limitation and about the severity of ischemia and prognosis especially in patients with an intermediate to high pre-test probability for CHD (8). Furthermore, the magnitude of coronary atherosclerosis is often underestimated on a luminal angiogram when these findings are compared with intravascular ultrasonographic studies (36). Thus, a coronary angiogram with only minor changes in arterial wall does not always eliminate the possibility that patient’s symptoms may be ischemic in origin. It is possible that vulnerable plaque which is not causing significant obstruction may lead an acute coronary event and the coronary spasm that is not visualised on the angiography may cause angina.

The ECG is monitored not only during exercise but also after exercise. The ECG should
be monitored for a several minutes after exercise. ST segment changes that were not apparent during exercise may occur during recovery period (30). It is not known whether such changes generally carry the same prognostic and diagnostic significance as those occurring during exercise. Some of the patients with ischemic ST abnormalities may not display such findings until reaching the recovery period (29,30,37). Multivessel or left main coronary artery disease has been found in approximately 90% of patients who have changes appearing at very low workloads and persisting for up to 8 minutes after exercise (10). With evidence available, the time necessary for resolution of ST segment depression correlated with severity myocardial ischemia, although this response is dependent on the indications for termination of exercise.

The least common form of silent myocardial ischemia occurs in totally asymptomatic patients with CHD (38). Epidemiological studies of sudden cardiac death, as well as clinical and post-mortem studies of patients with silent myocardial infarction, and studies of patients with suspected CHD suggest that many patients with coronary artery obstruction never experience angina pectoris in any of its recognized forms. These patients may be considered to have defective anginal warning system (38). The second form of silent ischemia occurs in patients with documented previous myocardial infarction. The third and much more frequent form occurs in patient with the combination of usual forms of chronic stable angina, unstable angina and Prinzmetal angina. The total ischemic burden in these patients refers to total period of ischemia, both symptomatic and asymptomatic.

The occurrence of silent myocardial ischemia in asymptomatic middle-aged men subjects has been estimated to be about 2.5 % under 60 years to 10 % above 70 years (39) and the corresponding number after acute myocardial infarction has been noted to be about 20 % to 40 % (38). Silent ischemia has been found in almost all patients of those with symptomatic CHD (38). Some studies have noted that the majority of ischemic episodes during daily life are not associated with symptoms indicating that about 75 % of all ischemic episodes are silent (40). The angina symptom is subjective and it has been found that about 50 % of episodes identified by the patients as typical angina are accompanied by ST segment changes. A diurnal variation has been described in coronary events, as the onset of acute myocardial infarction is noted with the highest frequency in the morning, but there may be
a smaller peak in the evening (41).

Some other situations appear to give rise to exercise-induced ST depression in the absence of obstruction to the coronary arteries. Mechanical changes that place a greater burden on left ventricular dynamics and oxygen requirements include such abnormalities as mitral or aortic valvular dysfunction, pulmonary hypertension, pericardial constriction, and left ventricular hypertrophy. Relative coronary insufficiency during exercise is probably also the responsible mechanism in patients with left ventricular hypertrophy. Patients with increased left ventricular mass, even in the absence of standard ECG voltage criteria for this diagnosis, may have false-positive ECG exercise responses (7, 8, 10, 42). This group of patients, however, may also have resting ST depression which increases during exercise indicating myocardial ischemia.

A wide variety of miscellaneous situations have also been associated with falsely positive ST responses to exercise. Some changes in T waves and ST-segment depression with hyperventilation and postural changes are relatively common and are mediated through autonomic nervous system. Other similar type of changes in ECG may be due to digitalis administration, hypokalemia, postprandial changes, vasoregulatory abnormalities and conduction defect (10). There is undoubtedly no common mechanism for ST changes in these diverse situations, however, effects brought about by electrolyte shifts and sympathetic nervous stimulation at the cellular level may play an important role (7, 8, 10).

2.6 Blood pressure responses during exercise

The monitoring of blood pressure at each incremental workload and during recovery is an essential part of exercise testing. The measurement of blood pressure during exercise has been documented as a reasonably accurate method, although the reliability of sphygmomanometer in recording arterial pressure during maximal exercise is questioned (43). It is not very easy to detect to Korotkoff sounds during exercise, especially when the subject is walking or jogging (44), and thus systolic blood pressure is generally easier to define than diastolic blood pressure during exercise. Secondly, it may be less accurate to measure systolic blood pressure at maximal exercise than at submaximal workloads. It is
sometimes difficult to obtain an accurate definition of systolic blood pressure due to body movements related to high level of exercise at maximal effort (45). However, blood pressure is usually measured indirectly by cuff sphygmomanometer rather than directly by using invasive methods. Furthermore, the invasive measurements of blood pressure may disturb the patient and generate vasoconstriction which also limits the use of invasive measurements.

During dynamic exercise, mean blood pressure differences between intra-arterial and noninvasive determinations are quite similar to those at rest. Systolic blood pressure recorded intra-arterially and by sphygmomanometer have been similar during exercise at angina pectoris threshold (44). However, disagreement between intra-arterial and automatically derived blood pressure may increase during exercise as compared with blood pressure differences observed at rest. It is reported that systolic blood pressure during exercise was underestimated when indirect method has been used as compared with intra-arterial measurements (46). When the treadmill and cycle ergometer are compared, the increase in systolic blood pressure has been lower with treadmill testing at similar submaximal workloads (47).

Blood pressure during exercise is dependent on cardiac output and peripheral resistance. Resting cardiac output (5 to 6 L/minute) increases to as high as 20 to 25 L/minute during peak exercise, an increase proportional to the exercise workload. A heart is usually fairly well perfused if left ventricle can function well when ejecting against very high resistance during exercise. In response to the increased stroke volume and systolic contractile force, systolic blood pressure normally rises with increasing workloads. As exercise progresses, systolic blood pressure increases typically by at least 50 to 70 mmHg, whereas diastolic blood pressure remains almost unchanged as a result of vasodilatation and decreasing total peripheral resistance (48).

Resting systolic blood pressure is a major determinant of maximal systolic blood pressure during exercise. The correlation between resting and maximal systolic blood pressure has varied between 0.45 to 0.68 (44). Maximal systolic blood pressure has been found to be higher in the hypertensive patients. Age, gender, body weight, cardiorespiratory fitness and cardioactive medications have been shown to affect the blood pressure response to exercise
The total rise in systolic blood pressure was the lowest among older and hypertensive persons as well as subjects with CHD, while older men with CHD have smaller increases in blood pressure during exercise.

Exercise capacity may cause variation in systolic blood pressure response to exercise. Fit subjects may have higher maximal systolic blood pressure and higher total systolic blood pressure rise due to their better exercise capacity (50), although there may also exist genetic variation in systolic blood pressure response to exercise (51). Normally, trained subjects achieved a significantly higher maximal systolic blood pressure during exercise compared with untrained subjects (49). The higher systolic blood pressure in trained individuals is a normal adaptive response that is due to increased cardiac output, and may be required to vital organs under the conditions of low systemic vascular resistance, while in the untrained subjects increased total peripheral resistance is the most likely mechanisms for high systolic blood pressure (49). Peripheral resistance during exercise may be an important factor related to the increased risk of CVD (50). However, it is also found that high fit individuals showed a slower rate of rise of systolic blood pressure during exercise as compared with those who had the moderate to low fitness levels (49).

An inadequate rise or a fall in systolic blood pressure is not a normal response to exercise. An inadequate rise in systolic blood pressure can result from aortic outflow obstruction, severe left ventricular dysfunction, myocardial ischemia, and certain types of drug therapy (i.e. β-blockers). In most studies, exercise-induced hypotension in association with other measures of ischemia predicts a poor prognosis, with a high positive predictive value for left main coronary artery disease or three-vessel CHD. Systolic hypotension during exercise is usually associated with global and regional left ventricular dysfunction, and is a marker of very severe CHD (7, 52). Exercise-induced hypotension is also associated with cardiac complications during exercise testing and can occur in subjects with CHD, cardiac arrhythmias, vasovagal reactions, left ventricular outflow tract obstruction, valvular heart disease, or cardiomyopathy. Occasionally, subjects without clinically significant CHD will exhibit exercise-induced hypotension during exercise related to dehydration or prolonged strenuous exercise.
2.7 Cardiorespiratory fitness and cardiovascular risk

Physical inactivity and low cardiorespiratory fitness are considered to be crucial health problems (53). Both of them have been associated with an increased risk of premature death in large prospective studies (54-63).

Table 1a. Physical fitness and mortality: population-based cohort studies

<table>
<thead>
<tr>
<th>Study population</th>
<th>Fitness measurement</th>
<th>Fitness categories</th>
<th>Follow-up time</th>
<th>Main result</th>
</tr>
</thead>
<tbody>
<tr>
<td>U.S. Railroad study (1988)(^\text{58}) (n=3043)</td>
<td>Submaximal heart rate, treadmill</td>
<td>most fit fourth vs. least fit fourth</td>
<td>20 years</td>
<td>1.2-fold risk for unfit men</td>
</tr>
<tr>
<td>Lipid Research Clinics Prevalence study (1988)(^\text{35}) (n=4276)</td>
<td>Submaximal heart rate, treadmill (modified Bruce protocol)</td>
<td>change in heart rate</td>
<td>8.5 years</td>
<td>2.7-fold adjusted risk for 2 SD increase in heart rate (17 beats/minute)(^*)</td>
</tr>
<tr>
<td>Cooper Clinics study (1989)(^\text{34}) (n=13344)</td>
<td>Exercise duration, treadmill (modified Balke protocol)</td>
<td>least fit quintile vs all other quintiles</td>
<td>8.0 years</td>
<td>1.6-fold adjusted risk for unfit men and women</td>
</tr>
<tr>
<td>Study of Norwegian men (1993)(^\text{57}) (n=2014)</td>
<td>Maximal workload, electrically braked cycle ergometer</td>
<td>least fit fourth vs. most fit fourth</td>
<td>16 years</td>
<td>50% decrease in adjusted risk for most fit men</td>
</tr>
<tr>
<td>The St. James Women Take Heart project (2003)(^\text{68}) (n=5721)</td>
<td>Treadmill exercise (Bruce protocol)</td>
<td>1 MET increment</td>
<td>8.4 years</td>
<td>17% decrease in adjusted risk for women</td>
</tr>
<tr>
<td>Lipid Research Clinics Prevalence study (2003)(^\text{97}) (n=2994)</td>
<td>Heart rate, near-maximal treadmill exercise (modified Bruce protocol)</td>
<td>1 MET decrement</td>
<td>20 years</td>
<td>1.2-fold age-adjusted risk change for women(^*)</td>
</tr>
</tbody>
</table>

\(^*\) Main outcome measure was cardiovascular mortality, SD denotes standard deviation. The MET is the ratio of the metabolic rate during exercise to the metabolic rate at rest. One MET is equivalent to 3.5 mL of oxygen consumption (\(\text{VO}_2\)) per kilogram of body weight per minute.
Evidence of the level of cardiorespiratory fitness needed to reduce premature mortality is based on a few population studies in U.S. (54, 55, 58, 64, 65) and Europe (57). Low cardiorespiratory fitness (54, 55, 57-61, 64-70) has been a strong predictor for mortality in apparently healthy and clinical populations (Table 1a-b). The high risk has been mainly due to an increased cardiovascular mortality in unfit individuals (54, 55, 57). A low cardiorespiratory fitness has been found to be as strong a predictor of mortality as the conventional modifiable risk factors, such as cigarette smoking, hypercholesterolemia and hypertension (60, 65, 69). In some studies, exercise capacity exhibited the strongest association with all-cause mortality and acute coronary events in both sexes (59, 60).

Table 1b. Physical fitness and mortality; clinical populations

<table>
<thead>
<tr>
<th>Study population</th>
<th>Fitness measurement</th>
<th>Fitness categories</th>
<th>Follow-up time</th>
<th>Main result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olmsted Country, Minnesota (1998)\textsuperscript{99} (n=2193)</td>
<td>Workload, treadmill (Bruce, modified Bruce or Naughton protocol)</td>
<td>1 MET increment</td>
<td>6.3 years</td>
<td>17 to 23 % decrease in adjusted risk</td>
</tr>
<tr>
<td>Belgian study (1994)\textsuperscript{96} (n=527)</td>
<td>Peak VO\textsubscript{2}, cycle exercise test</td>
<td>decrease of 1 litre in minute of oxygen uptake</td>
<td>6.1 years</td>
<td>57 % decrease in adjusted risk</td>
</tr>
<tr>
<td>Olmsted Country, elderly population, Mayo Clinic (2000)\textsuperscript{101} (n=3107)</td>
<td>Workload, work capacity, treadmill</td>
<td>1 MET increment</td>
<td>6.0 years</td>
<td>18 % decrease in adjusted risk</td>
</tr>
<tr>
<td>Clinical population, Standford (2002)\textsuperscript{90} (n=3679)</td>
<td>Exercise duration, treadmill (graded or ramp protocol)</td>
<td>1 MET increment</td>
<td>6.2 years</td>
<td>12 % decrease in age-adjusted risk</td>
</tr>
<tr>
<td>Patients with acute myocardial infarction DANAMI-2* study (2005)\textsuperscript{90} (n=1164)</td>
<td>Workload, cycle exercise test</td>
<td>1 MET increment</td>
<td>3.1 years</td>
<td>18 % decrease in adjusted risk</td>
</tr>
</tbody>
</table>

*the second Danish trial in acute myocardial infarction

The MET is the ratio of the metabolic rate during exercise to the metabolic rate at rest. One MET is equivalent to 3.5 mL of oxygen consumption (VO\textsubscript{2}) per kilogram of body weight per minute
Previous population-based studies have also found an association of physical activity and cardiorespiratory fitness with the incidence of CHD (63, 71-74). Additional evidence for the antiatherogenic effect of regular physical activity and good cardiorespiratory fitness is derived from clinical trials, which have shown that physical activity alone (75, 76) or combined with low-fat diet (77, 78) or comprehensive lifestyle modification (79) with concomitant improvement in cardiorespiratory fitness retards the progression of angiographically or ultrasonographically quantified atherosclerosis. Furthermore, low VO_{2max} has been established to be a strong independent risk factor for acute myocardial infarction (71). Physically fit patients with multi-vessels coronary artery disease, who achieved 10 METs during exercise test, had an excellent survival rate whereas a low exercise capacity of less than 6 METs indicates a higher mortality, regardless of the extent of coronary atherosclerosis or left ventricular function (80). Even patients with angiographically defined three-vessel disease, who achieved a minimum exercise capacity of 7 to 10 METs, had an excellent survival (80), whereas patients with ST elevation acute myocardial infarction had a very good prognosis, if exercise capacity was over 8 METs after fibrinolysis therapy or primary angioplasty (70). In a subgroup who were treated by primary angioplasty (70), exercise capacity seems to add prognostic information, although exercise-induced ST depression did not have a prognostic value. On the other hand, a negative result in ECG stress test with a high exercise capacity indicates a good progress, it does not necessarily always imply the absence of coronary artery disease.

Current recommendations showing the level of cardiorespiratory fitness needed to reduce premature mortality are based on a few prospective population-based studies (62, 63). Previous population studies are based on indirect definition of cardiorespiratory fitness whereas only a few studies have used the direct assessment of VO_{2max} (60). There are no other previous cohort studies that are based on directly measured cardiorespiratory fitness during exercise testing and the risk of all-cause and CVD death.
2.8 Silent myocardial ischemia and cardiovascular risk

Painless myocardial ischemia has long been recognized as a common finding in patients with CHD (82) and diabetes (83). Myocardial ischemia during exercise is a well established predictor of pathophysiologically significant CHD (84). Exercise testing is widely used as a diagnostic test in the initial evaluation of patients with symptoms suggestive of myocardial ischemia and in persons with previously recognized CHD (29). Exercise-induced ischemic ST changes have been associated with increased risk of acute coronary events not only in patients with established CHD but also in asymptomatic individuals (85-91). Some studies (39, 82, 92) have indicated that painless, or silent, and painful myocardial ischemia have a similar prognostic value, whereas others (91) have suggested that symptomatic ischemia is a stronger risk factor for acute coronary events and cardiovascular death in patients with CHD. However, there are few if any previous data showing that ischemic ST changes during exercise and recovery would have long-term prognostic value in asymptomatic subjects.

Although exercise testing has been applied and studied as a screening or prognostic test in asymptomatic persons, the implications of ischemic ECG findings have not been well defined in various risk groups (29). The magnitude of the prognostic value of an abnormal exercise ECG without pain may vary considerably because of different inclusion criteria for the subjects in previous studies (90, 91). The clinical importance and prognostic significance of silent myocardial ischemia during exercise and recovery in asymptomatic high-risk persons remains controversial (85, 90). There are no previous studies that would have addressed the question whether existence of at least one conventional risk factor, such as smoking, hypercholesterolemia and elevated blood pressure at rest, increases the risk of acute coronary events and CHD death.

In the Lipid Research Clinics Coronary Primary Prevention Trial (82), hypercholesterolemic men with >1 mm ST depression on exercise testing had almost a 6 times greater risk of death from CHD than those with a negative test. Interestingly, a positive test was not significantly associated with the risk of a non-fatal myocardial infarction. The Multiple Risk Factor Intervention Trial (92) reported a nearly 4-fold
increase in CHD mortality among men with an abnormal exercise ECG and suggested that the exercise ECG might serve to identify high-risk men who could benefit from risk factor reduction.

The routine use of exercise ECG in completely unselected asymptomatic populations before office screening for risk has not been recommended, and the role of ischemic ST changes in the CHD risk prediction is a controversial issue in apparently healthy individuals. However, the exercise-induced ST segment depression can identify the subgroup with increased risk of future coronary event and cardiac death. In asymptomatic men >40 years old with ≥1 risk factor, exercise testing may provide useful information as a guide to aggressive risk factor intervention or the need to further evaluate the cause of myocardial ischemia. In the Seattle Heart Watch Study (91), men with one or more risk factors (positive family history, smoking, hypertension, and hypercholesterolemia) and 2 abnormalities on exercise testing (chest pain, exercise duration <6 minutes, ST depression >1.0 mm, or <90% predicted heart rate) had a very high CVD risk.

The results in previous reports emphasizing the prognostic significance of myocardial ischemia in asymptomatic individuals have led the American Heart Association and the American College of Sports Medicine to recommend that apparently healthy men age ≥45 years and women ≥ 55 years should undergo a maximal exercise test before engaging in a vigorous exercise program, especially in subjects with high risk for CHD or other atherosclerotic vascular diseases (7, 8, 93). Also, among unfit subjects with multiple risk factors, exercise testing can be used as a guide for risk reduction therapy. Patients with diabetes who wish to enroll in moderate-to-high-intensity exercise program are considered to have a good supportive evidence for exercise testing (7, 8). However, data are quite limited regarding the prognostic utility of noninvasive measures of inducing myocardial ischemia in apparently asymptomatic persons (3). Therefore, conclusions about the role of exercise testing for the purpose of risk assessment are limited.
2.9 Exercise blood pressure and cardiovascular risk

2.9.1 Exercise blood pressure in apparently healthy populations
Systolic blood pressure changes at different workloads during an exercise test correspond to blood pressure changes in daily physical stress conditions (49, 94). Exercise-induced elevation in systolic blood pressure has been found to increase the risk of future hypertension (95-97), left ventricular hypertrophy (98, 99), cerebrovascular stroke (100) and CVD death (101, 102). An abnormal rise in exercise systolic blood pressure in a subject with a normal resting pressure predicts an increased risk for future hypertension (95).

An increase of systolic blood pressure during an exercise test at a moderate workload predicted higher CVD mortality than systolic blood pressure at rest (101, 102), whereas exercise systolic blood pressure at moderate workloads had limited value in the evaluation of CVD risk compared with resting systolic blood pressure in hypertensive patients (94). In a large prospective study (101), the magnitude of exercise-induced elevation of systolic blood pressure (over 230 mmHg) was related to an increased risk of death from CVD showing the evidence that an exaggerated response in normotensive subjects may be of prognostic value. It is not known whether treatment of elevated exercise systolic blood pressure alters the progression of the underlying physiological abnormalities in hypertension or improves the prognosis. However, exercise testing can identify persons with exaggerated systolic blood pressure response during and after exercise, indicating future risk for developing hypertension and increased CVD mortality.

2.9.2 Exercise blood pressure in individuals with cardiovascular disease
Previous studies have revealed that blood pressure achieved during maximal exercise is dependent on underlying coronary artery disease (44). Some studies have shown that elevated systolic blood pressure during exercise may indicate a lower probability of severe coronary artery disease and better prognosis in patients with known or suspected CHD (103-105). There was a significant trend toward a lower rate of subsequent mortality in men with higher systolic blood pressure during the exercise test (44). Maximal systolic blood pressure is correlated with the number of obstructed coronary arteries and also with
ejection fraction showing the anatomical explanation. This suggests that the increased blood pressure response identified among subjects with good left ventricular function could thus generate higher blood pressures with increasing workloads.

Abnormal resting ECG changes (Q-waves, ST depression) are more common among men with the lowest maximal systolic blood pressure during exercise (44). Previous studies that indicate a poorer prognosis of persons with lower exercise blood pressures is a consequence of their severe CHD, previous myocardial infarction and abnormal left ventricular function (44). They suggested high specificity of the small systolic blood pressure changes during exercise for future risk of death and for two and three vessels coronary artery stenosis. This means that exercise testing with systolic blood pressure measurements is valuable in defining the persons at the highest risk of death (104, 106).

It is also known that a decrease in blood pressure during exercise is related to the increased risk of CVD (7). Failure to increase systolic blood pressure by 10 to 30 mmHg or a decrease in systolic blood pressure during exercise has been shown to be an independent predictor of adverse outcome after acute myocardial infarction (107-109). Furthermore, inability to attain a systolic blood pressure greater than 110 mmHg has been shown to predict poor outcome in patients with Q-wave myocardial infarction (110). Failure to increase systolic blood pressure over 120 mmHg or a fall in systolic blood pressure below standing values at rest reflects inadequate elevation of cardiac output because of left ventricular systolic dysfunction (45, 110, 111).

2.9.3 Blood pressure during recovery from exercise
The rate of the systolic blood pressure drop during the first minutes of recovery period is usually fairly rapid after maximal exercise, although a rebound with a temporarily rise about 1 minute after exercise is observed (112). This finding is believed to be due to the recovery from the anaerobic metabolism that has occurred at peak exercise. It is also reported that systolic blood pressure in patients with coronary artery disease fails to drop as fast as in normal subjects or blood pressure even continue to rise immediately after exercise staying at high level during recovery from exercise (113).

Myocardial ischemia may reduce the rate of which systolic blood pressure level falls. It is
shown that a high level of systolic blood pressure after exercise in comparison with the peak systolic blood pressure level during exercise suggests the presence of ischemia (114-116). Such a retarded pressure drop is an insensitive indicator of ischemia, but it is fairly specific for this disorder. It may result from ischemic suppression of left ventricular function during exercise combined with the subsequent recovery of contractility during recovery. This response has been found usually to signal for extensive myocardial ischemia, with the systolic blood pressure increasing proportionally with the number of obstructed coronary arteries (115). Studies comparing blood pressures at 1 and 3 minutes after exercise (116) or maximal systolic blood pressure and systolic blood pressure at recovery (100) have shown the predictive value of blood pressure decrease after exercise with regard to the risk of CVDs. In some subjects with CHD, higher levels of systolic blood pressure exceeding peak exercise values have been observed during the recovery phase. It has been suggested that systolic blood pressure response is abnormal if the value at 3 minutes equalled or exceeded that at 1 minutes after exercise (116).

Because the recovery systolic blood pressure is dependent on the magnitude of exercise and systolic blood pressure at high workloads is difficult to record accurately, many investigators have been sceptical of the clinical usefulness of the ratio of exercise and recovery systolic blood pressure. However, it appears that if accurate measures of systolic blood pressure could be devised during cycle exercise testing, it would have prognostic value. An abnormal delay in the decrease in heart rate after exercise is suggested to be due to inadequate reaction of vagal tone because of an increase in activity of the sympathetic nervous system (26). Although blood pressure during recovery may also reflect cardiovascular reactivity after exercise, the prognostic value of systolic blood pressure after exercise has not been previously documented with respect to acute myocardial infarction.
2.10 Summary

Both treadmill and cycle exercise tests are widely accepted clinical testing methods with their typical advantages. Exercise capacity and ischemic ECG changes can be defined by using these testing methods. Indirectly defined cardiorespiratory fitness has been one of the strongest risk factors for CVD in previous studies. Exercise-induced painful and painless ischemia are risk predictors for ischemic cardiac events although the role of silent myocardial ischemia is not well known among men with coexisting risk factors. Exercise-induced blood pressure changes during exercise are important hemodynamic variables during cycle exercise testing. However, the prognostic value of systolic blood pressure immediately after maximal exercise testing is not well known with respect to acute myocardial infarction.

The specific aspects of testing methods, such as mode of exercise, analysis of respiratory gases and outcomes may depend on the population being tested. The measurement of functional capacity may provide a valuable noninvasive tool for the diagnostic and prognostic assessment in population studies and a wide variety of clinical settings, regardless of many recent advances in cardiac imaging. Recent evidence also suggests that even more attention should be focused on the recovery period using ECG and systolic blood pressure recordings after the cessation of maximal exercise.
3. AIMS OF THE STUDY

a) to examine the associations of cardiorespiratory fitness, as indicated by directly measured maximal oxygen uptake and exercise test duration, with mortality from CVD and all causes.

b) to study the associations of cardiorespiratory fitness with the risk of major cardiovascular outcomes among men with high and low pre-test probability for CHD.

c) to investigate the prognostic value of silent myocardial ischemia during and after exercise with regard to acute coronary events and mortality from CHD and whether coexistence of at least one conventional risk factor modifies these associations.

d) to explore the prognostic significance of systolic blood pressure changes during recovery from exercise with regard to acute coronary events and mortality from CVD.
4. METHODS

4.1 Study population

The study was carried out with the participants of the Kuopio Ischaemic Heart Disease Risk Factor Study (KIHD), an ongoing population study designed to investigate risk factors for CVD, atherosclerotic vascular diseases and related outcomes (117). The study involves men from eastern Finland, an area known for its high prevalence and incidence of atherosclerotic vascular diseases (118). The study group is a representative sample of men who lived in the town of Kuopio or its surrounding rural communities and were 42, 48, 54 or 60 years of age at baseline examinations between March 1984 and December 1989. Of 3235 eligible men, 2682 (83 %) participated in the study. The KIHD was approved by the Research Ethics Committee of the University of Kuopio, Kuopio, Finland. Each participant gave written informed consent. Table 2 shows the description of the follow-up studies including exercise testing and main outcomes.

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Population</th>
<th>Exercise test variable</th>
<th>Follow-up time</th>
<th>Main outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>1294</td>
<td>Without CVD (hypertensive included), cancer or pulmonary disease</td>
<td>Maximal oxygen uptake, exercise duration</td>
<td>10.7 years</td>
<td>42 CVD deaths 124 overall deaths</td>
</tr>
<tr>
<td>II</td>
<td>2361</td>
<td>Healthy and unhealthy (CVD, cancer, pulmonary disease)</td>
<td>Maximal oxygen uptake</td>
<td>13.7 years</td>
<td>323 acute coronary events 153 CHD deaths 204 CVD deaths 425 overall deaths</td>
</tr>
<tr>
<td>III</td>
<td>1769</td>
<td>Without CHD and typical angina pectoris</td>
<td>Painless myocardial ischemia in exercise electrocardiogram</td>
<td>10.2 years</td>
<td>174 acute coronary events 53 CHD deaths</td>
</tr>
<tr>
<td>IV</td>
<td>2336</td>
<td>Healthy and unhealthy with exercise blood pressure measurement</td>
<td>Systolic blood pressure during exercise testing</td>
<td>13.1 years</td>
<td>358 acute myocardial infarctions 202 CVD death</td>
</tr>
</tbody>
</table>

CHD denotes coronary heart disease and CVD denotes cardiovascular disease
4.2 Exercise testing

Cardiorespiratory fitness, exercise-induced myocardial ischemia and blood pressure were assessed using a maximal, symptom-limited exercise tolerance test on an electrically braked cycle ergometer. For men examined before June 1986, the testing protocol comprised a three-minute warm-up at 50 W followed by a step-by-step increase in the workload of 20 W per minute (Tunturi EL 400, Turku, Finland). The remaining men were tested with a linear increase in the workload of 20 W per minute (Medical Fitness Equipment 400L, Mearn, Netherlands).

4.3 Assessment of cardiorespiratory fitness

VO\text{2max} and exercise test duration were used as measures of cardiorespiratory fitness. Respiratory-gas exchange was measured for the first 622 men by the mixing-chamber method (Gebr., Mijnhart B.V., Netherland), and for the other 1739 men by a breath-by-breath method (Medical Graphics, St. Paul, Minnesota, U.S.A.). VO\text{2max} was defined as the highest value for or the plateau of oxygen uptake. VO\text{2max} was also expressed in METs.

4.4 Assessment of exercise electrocardiography

ECG was recorded continuously with the Kone 620 electrocardiograph (Kone, Turku, Finland). The Mason-Likar lead system including V1, V5 and aVF lead connections was used (37). ECG was printed every 30 seconds intervals during exercise and at least five minutes of recovery while the subject was sitting on the bicycle. Exercise ECGs were coded manually by one cardiologist.

The criteria for ischemia in ECG during exercise and recovery were horizontal or downsloping ST depression with 1.0 or more mm at 80 msec after J point or any ST depression of more than ≥1.0 mm at 80 msec after J point. Silent myocardial ischemia during exercise and after 5 minutes of recovery was defined as ischemia in the ECG without typical chest pain indicating CHD.
4.5 Assessment of exercise blood pressure

Pre-exercise blood pressure was measured manually when a subject was sitting on the cycle ergometer immediately before the test, and blood pressure was measured every two minutes during and after the exercise test using cuff stethoscope method. The maximal systolic blood pressure was the highest value achieved during the test. Blood pressure was measured during recovery at regular 2 minutes intervals while subjects seated on the cycle without pedaling (100). Of these post-exercise measurements, systolic blood pressure at 2 minutes recovery was selected as the main variable because it was available for all men. The systolic blood pressure difference between rest and recovery was calculated as systolic blood pressure at recovery from exercise minus systolic blood pressure at rest.

4.6 Biochemical analyses

Fasting blood glucose was measured using the glucose dehydrogenase method (Merck, Darmstadt, Germany) after proteins had been precipitated with trichloroacetic acid. Fasting serum insulin was measured with a radioimmunoassay (Novo, Biolabs, Novo Nordisk, Bagsvaerd, Danmark). The cholesterol contents of serum lipoprotein fractions and triglycerides were measured enzymatically (Boehringer Mannheim, Mannheim, Germany). Serum HDL cholesterol and its subfractions were separated from fresh serum samples using ultracentrifugation and precipitation (119). Plasma fibrinogen was determined based on clotting of diluted plasma with excess thrombin using a Goagulometer KC4 device (Heinrich Amelung, Lemgo, Germany).

4.7 Resting blood pressure

Resting blood pressure was measured between 8:00 and 10:00 a.m. by two trained nurses, one during 1984 to 1985 and another during 1986 to 1989, with a random-zero sphygmomanometer (Hawksley, Lancing, U.K.). The measurement protocol included six measurements with five minutes' intervals in the supine, standing and sitting positions.
Resting blood pressure was measured by an experienced nurse using a random-zero sphygmomanometer after 5 and 10 minutes of rest in a seated position between 8:00 a.m. and 10:00 a.m. a week earlier than the exercise stress test (120).

4.8 Overweight and obesity

Body mass index (BMI) was computed as weight in kilograms divided by the square of height in meters. Subjects with a BMI $\geq 25$ m/kg$^2$ were considered as an overweight. Waist-to-hip ratio was computed as the ratio of the circumference of the waist to the hip.

4.9 Smoking and alcohol consumption

The current number of cigarette, cigars, and pipefuls of tobacco smoked daily and the duration of regular smoking in years were recorded using a self-administered questionnaire. Years smoked were defined as the sum of the years of smoking, or whether it had occurred continuously or during several periods. The lifelong exposure to smoking was estimated as the product of years smoked and the number of tobacco products smoked daily at the time of the examination, or for ex-smokers, at the time when they had smoked last time. Alcohol consumption was assessed with a structured quantity-frequency method using the Nordic Alcohol Consumption Inventory on drinking behaviour over the previous 12 months and from dietary record over four days.

4.10 Physical inactivity

Physical activity was assessed using the KIHD 12-Month Leisure-Time Physical Activity Questionnaire (71). This detailed quantitative questionnaire deals with the most common physical activities of middle-aged Finnish men and enables the assessment of all components of physical activity. For each activity performed, the subject were asked to record the frequency (number of sessions per month), average duration (hours and minutes per session), and intensity (scored as 0 for recreational activity, 1 for conditioning activity,
2 for brisk conditioning activity, 3 for competitive, strenuous exercise). A trained nurse checked and completed the questionnaire in an interview.

4.11 Baseline cardiovascular diseases and medications

Medical history, the use of medications and family history of diseases were assessed using self-administered questionnaires. Information about medical history and the use of medications were checked during a medical examination. Prevalent CHD was defined as having either a history of myocardial infarction, angina pectoris on effort or the use of nitrolycerin for chest pain once a week or more frequently. The prevalent CVD was defined as a history of CHD, hypertension, congestive heart failure, cardiomyopathy, arrhythmias, stroke or claudication.

A family history of CHD was defined as premature CHD in parents or in the first degree relatives before the age of 55 in men or the age of 65 in women. Diabetes was defined as fasting blood glucose of over or equal to 6.7 mmol/l or a clinical diagnosis of diabetes with either dietary, oral or insulin treatment.

4.12 Collection and classification of follow-up events

4.12.1 Mortality

All deaths were ascertained by linkage to the National Death Registry using the Finnish personal identification code. Deaths that occurred between study entry (March, 1984 to December, 1989) and to the end of follow-up were included. Deaths were ascertained by computer linkage to the National death registry using the social security number. There were no losses to follow-up. Deaths from CVD and CHD were coded using to the Ninth International Classification of Diseases (ICD) codes (390-459 and 410-414, respectively) or the Tenth ICD codes (100-199 and I20-I25, respectively).
4.12.2 Acute coronary events

The collection of data on and the diagnostic classification of non-fatal and fatal coronary events by the end of 1992 were carried out as a part of the multinational WHO MONICA (MONItoring of Trends and Determinants in CArdiovascular Diseases) project, in which detailed information of all coronary events and strokes were collected prospectively (121). At baseline, all KIHD participants lived in the province of Kuopio, one of the monitoring areas of the Finnish part of the WHO MONICA project (FINMONICA) (122). In the FINMONICA study, regional coronary register teams collected data on coronary events from hospitals and wards of health centers and classified the events (122). The sources of information were interviews, hospital documents, death certificates, autopsy reports and medico-legal reports. The diagnostic classification of coronary events was based on symptoms, electrocardiographic findings, cardiac enzyme elevations, autopsy findings and history of CHD.

Each suspected coronary event (ICD-9 codes 410-414 and ICD-10 codes I20-I25) was classified into 1) a definite acute myocardial infarction, 2) a probable acute myocardial infarction, 3) a typical acute chest pain episode of more than 20 minutes indicating CHD, 4) an ischemic cardiac arrest with successful resuscitation, 5) no acute coronary event or 6) an unclassifiable fatal case. The FINMONICA coronary register data were annually cross-checked with the data obtained from the computerized national hospital discharge and death registers. Data on non-fatal and fatal coronary events from the beginning of 1993 to the end of 2001 were obtained by computer linkage to the national hospital discharge and death certificate registers. A physician collected and classified the coronary events using the same procedures as in the FINMONICA study (122). Definite and probable acute myocardial infarctions and prolonged chest pain episodes were used as outcome events. All chest pain episodes lead to hospitalization. If a subject had multiple non-fatal coronary events during the follow-up, the first was considered as the end point.
4.13 Statistical methods

Statistical analyses were performed using the SPSS 11.5 for Windows (SPSS, Inc., Chicago, Illinois). Descriptive data are presented as mean and standard deviations for continuous data and percentages for categorical data. Differences in baseline characteristics were examined using independent samples t-test and the chi-squared test. The correlations between risk factors of interest were analyzed using Pearson's correlation test. The association of exercise testing variables with the risk of outcomes were analyzed using Cox proportional hazards' models. Relative hazards (95 % confidence intervals, CIs), adjusted for risk factors, were estimated as antilogarithms of coefficients from multivariable models. The fit of the proportional-hazards' models was examined by plotting the hazard functions in different categories of risk factors over time. The cumulative incidence of acute coronary events and mortality was calculated using the Kaplan-Meier method. Tests for statistical significance were two-sided. A value of p less than 0.05 was considered statistically significant.

4.13.1 Study I

The associations of cardiorespiratory fitness with the risk factors for death were examined using covariate analysis. The levels of VO$_{2\text{max}}$ and exercise test duration were entered into forced Cox proportional hazards' models where men in the highest quartile of cardiorespiratory fitness represented the reference group. Three different sets of covariates were used: 1) age and examination year 2) age, examination year, cigarette smoking and alcohol consumption and 3) age, examination year, cigarette smoking, alcohol consumption, systolic blood pressure, diabetes, fasting serum insulin, plasma fibrinogen, and serum HDL and LDL cholesterol and triglycerides.

4.13.2 Study II

In Cox proportional hazards models, VO$_{2\text{max}}$ was entered into forced Cox proportional hazards' models by using VO$_{2\text{max}}$ as a continuous variable as well as categorised in quartiles. The least 25 % of men were defined as unfit, 25 to 75 % of men were moderate fit and the
remaining 25% as most fit. The cut-off values for VO2max among both healthy and unhealthy groups were based on the group-specific quartiles of VO2max. In these analyses, the reference group was the highest quartile (most fit group). Cox regression models were adjusted for age and examination year, and other risk factor (cigarette smoking, alcohol consumption, diabetes, waist-to-hip ratio, fasting serum insulin, plasma fibrinogen, serum HDL and LDL cholesterol and triglycerides, systolic and diastolic blood pressure), the use of anti-hypertensive medication, aspirin or lipid lowering drugs and exercise-induced myocardial ischemia. Hypertension was defined as systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg at rest and overweight were those men with BMI ≥25 m/kg². The analyses were performed among men with high (unhealthy) and low (healthy) pre-test probability for the cardiovascular events.

4.13.3 Study III
The study was based on men without prevalent CHD or angina pectoris symptoms during exercise test. The associations of silent myocardial ischemia during exercise and recovery with the risk of acute coronary events and CHD death were analyzed using risk factor (age, cigarette smoking, systolic blood pressure, alcohol consumption, BMI, VO2max, diabetes and serum LDL and HDL cholesterol) adjusted Cox proportional hazards' models. The modification of the prognostic value of silent myocardial ischemia by the major CHD risk factors was analyzed by comparing smokers and non-smokers, men with higher (≥3.9 mmol/L, median) and lower (<3.9 mmol/L) serum LDL cholesterol and men with higher (≥132.3 mmHg, median) and lower (<132.3 mmHg) systolic blood pressure.

4.13.4 Study IV
The associations of systolic blood pressure during the exercise test with the risk of acute myocardial infarction and CVD death were analyzed using multivariable Cox proportional hazards' models. To demonstrate the prognostic value of exercise systolic blood pressure, it was entered with and without resting systolic blood pressure into multivariable models including age, examination year, the use of antihypertensive medication, and other covariates (alcohol consumption, cigarette smoking, serum HDL and LDL cholesterol,
serum triglycerides, diabetes, BMI, myocardial ischemia demonstrated on the ECG during exercise, $VO_2_{\text{max}}$ and maximal heart rate). In additional multivariable models, diastolic blood pressure at rest and recovery were also included with these covariates.
5. RESULTS

5.1 Baseline characteristics

The most important demographic and biochemical characteristics of men according to baseline health status are presented in Table 3. The mean age of the subjects was 52.9 (standard deviation 5.1) years. Hypertension was diagnosed in 24% for asymptomatic men (healthy group) and 38% for unhealthy men, respectively. Men with known CVD were older and the levels of conventional risk factors tended to be higher than those without CVD. Most common CVDs included CHD and hypertension and many subjects had a positive family history of CHD and hypertension.

An average resting systolic blood pressure was 134 mmHg and diastolic blood pressure was 89 mmHg. A total proportion of men who were using β-blockers was 17.2%, whereas the use of ACE-inhibitors and calcium channel blockers was low. The number of smokers did not markedly differ among these groups of men, and the mean values of serum total and LDL cholesterol were high in both groups. The use of lipid lowering medication was not very common at the time of baseline examination. Mean BMI values were 26.6 kg/m² in healthy men and 27.1 kg/m² in unhealthy men, respectively. Fasting blood glucose and serum insulin levels and the prevalence of diabetes were higher in men with known CVD.

The total amount of conditioning leisure time physical activity (energy expenditure) did not differ between healthy and unhealthy men. However, the mean intensity of physical activity (METs) was higher among men without known disease at baseline.
## Table 3. A cross-sectional comparison of the study population according to baseline health status.

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Healthy men (n=1294)</th>
<th>Unhealthy men (n=1057)</th>
<th>P for difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>51.8 (5.4)</td>
<td>54.2 (4.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.6 (3.4)</td>
<td>27.1 (3.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>0.94 (0.06)</td>
<td>0.96 (0.06)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smokers, %</td>
<td>31.4</td>
<td>32.6</td>
<td>0.537</td>
</tr>
<tr>
<td>Cigarette smoking, pack-years*</td>
<td>7.95 (16.0)</td>
<td>8.98 (17.1)</td>
<td>0.138</td>
</tr>
<tr>
<td>Alcohol consumption, g/week</td>
<td>70.9 (109.4)</td>
<td>79.8 (139.3)</td>
<td>0.255</td>
</tr>
<tr>
<td>Physical activity, kcal/week †</td>
<td>982.2 (1151.1)</td>
<td>972.3 (1306.4)</td>
<td>0.848</td>
</tr>
<tr>
<td>Mean intensity of physical activity, METs †</td>
<td>5.98 (1.80)</td>
<td>5.53 (1.75)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum total cholesterol, mmol/L</td>
<td>5.86 (1.02)</td>
<td>5.96 (1.12)</td>
<td>0.024</td>
</tr>
<tr>
<td>Serum LDL; ‡ cholesterol, mmol/L</td>
<td>4.01 (0.97)</td>
<td>4.09 (1.06)</td>
<td>0.064</td>
</tr>
<tr>
<td>Serum HDL; ‡ cholesterol, mmol/L</td>
<td>1.31 (0.30)</td>
<td>1.27 (0.31)</td>
<td>0.001</td>
</tr>
<tr>
<td>Serum triglycerides, mmol/L</td>
<td>1.23 (0.76)</td>
<td>1.36 (0.88)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>133.8 (16.1)</td>
<td>134.4 (17.8)</td>
<td>0.392</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>88.8 (10.4)</td>
<td>88.9 (10.6)</td>
<td>0.803</td>
</tr>
<tr>
<td>Fasting blood glucose, mmol/L</td>
<td>4.70 (0.89)</td>
<td>4.85 (1.45)</td>
<td>0.004</td>
</tr>
<tr>
<td>Serum insulin, µU/L</td>
<td>10.8 (5.6)</td>
<td>12.6 (8.2)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

### Diagnosed diseases

- **Coronary heart disease, %**: 23.8
- **History of myocardial infarction, %**: 7.4
- **Family history of coronary heart disease, %**: 44.8
- **Abnormal resting ECG findings, %**: 7.3
- **Coronary by-pass surgery, %**: 0.6
- **History of hypertension, %**: 24.0
- **Family history of hypertension, %**: 45.1
- **Cardiac insufficiency, %**: 6.6
- **Cardiomyopathy, %**: 2.1
- **Cerebrovascular disease, %**: 2.4
- **Claudication, %**: 3.8
- **Arrhythmias, % ‡**: 15.8
- **Chronic obstructive pulmonary disease, %**: 7.0
- **Bronchial asthma, %**: 3.3
- **Pulmonary tuberculosis, %**: 3.8
- **Cancer, %**: 1.6
- **Diabetes, %**: 4.6

### Regular use of medications

- **Anti-hypertensive medication, %**: 10.4
- **Medication for hypercholesterolemia, %**: 1.5
- **β-blocker, %**: 7.8
- **Acetylsalicylic acid, %**: 5.2

* Pack-years denotes the lifelong exposure to smoking which was estimated as the product of years smoked and the number of tobacco products smoked daily.
† Conditioning physical activity was assessed using the 12-month Leisure Time Physical Activity Questionnaire (71).
‡ LDL denotes low-density lipoprotein and HDL denotes high-density lipoprotein.
§ Arrhythmias included extrasystolia, regular or paroxysmal atrial fibrillation and supraventricular tachycardia.
¶ Unhealthy men had CVD (excluding hypertension), pulmonary disease or cancer at baseline.
5.2 Exercise test findings

Men without CVD at baseline had a higher VO\textsubscript{2max}, maximal heart rate and maximal systolic blood pressure (Table 4). The mean of VO\textsubscript{2max} was 32.5 mL/kg/minute (range 16.0 to 65.4 mL/kg/minute) and the mean exercise test duration was 9.8 minutes (range 2.9 to 19.9 minutes) during cycle exercise test among healthy men. The respective mean values were 27.3 mL/kg/minute (range 7.4 to 51.9 mL/kg/minute) and 7.9 minutes (range 1.5 to 16.2 minutes) among unhealthy men. Systolic blood pressure immediately after exercise did no differ statistically significantly although diastolic blood pressure after exercise was lower in men without CVD than in those without CVD. The ischemic ECG changes at baseline were more common among men with CVD than among those without CVD.

<table>
<thead>
<tr>
<th>Table 4. Characteristics of exercise testing in study population according to baseline health status.</th>
<th>Healthy men (n=1294)</th>
<th>Unhealthy (n=1057)</th>
<th>P for difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise test variables</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td></td>
</tr>
<tr>
<td>Maximal oxygen uptake, mL/kg/minute</td>
<td>32.5 (7.5)</td>
<td>27.3 (7.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Maximal oxygen uptake, mL/minute</td>
<td>2.57 (5.89)</td>
<td>2.18 (6.23)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Maximal oxygen pulse, mL/ beat</td>
<td>16.4 (10.2)</td>
<td>15.6 (11.8)</td>
<td>0.081</td>
</tr>
<tr>
<td>Maximal heart rate, beats/minute</td>
<td>162 (21)</td>
<td>145 (27)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Resting heart rate, beats/minute</td>
<td>62 (11)</td>
<td>62 (11)</td>
<td>0.926</td>
</tr>
<tr>
<td>Maximal systolic blood pressure, mmHg</td>
<td>206.9 (25.9)</td>
<td>197.4 (30.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SBP* at 2 minutes after exercise, mmHg</td>
<td>184.4 (27.8)</td>
<td>182.3 (27.8)</td>
<td>0.380</td>
</tr>
<tr>
<td>DBP* at 2 minutes after exercise, mmHg</td>
<td>89.8 (15.9)</td>
<td>93.4 (14.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Difference in SBP* at recovery and rest, mmHg †</td>
<td>54.4 (23.8)</td>
<td>51.8 (23.6)</td>
<td>0.007</td>
</tr>
<tr>
<td>Exercise-induced myocardial ischemia, % ‡</td>
<td>6.7</td>
<td>10.5</td>
<td>0.001</td>
</tr>
<tr>
<td>Peak respiratory gas exchange ratio (VCO\textsubscript{2}/VO\textsubscript{2})</td>
<td>1.12 (0.13)</td>
<td>1.06 (0.15)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* SBP denotes systolic blood pressure and DBP denotes systolic blood pressure.
† Difference in SBP was calculated as SBP at recovery from exercise minus SBP at rest.
‡ The criteria for myocardial ischemia in electrocardiogram were horizontal or downsloping ST depression 1.0 mm at 80 msec after J point or any ST depression of more than 1.0 mm at 80 msec after J point.
5.3 Cardiorespiratory fitness and mortality

5.3.1 Cardiorespiratory fitness and mortality among men without previous CVD

Low cardiopulmonary fitness was related to an increased risk of all-cause and CVD death (Figure 1a - b). Men in the lowest quartile of VO2max (<27.6 mL/kg/min, 7.9 METs) had a 2.76 (95% CI 1.43 to 5.33, p=0.002) times higher risk of overall mortality than men in the highest quartile of VO2max (>37.1 mL/kg/min, 10.6 METs) after adjusting for age, examination years, smoking and alcohol consumption. The risk of overall death was 2.72-fold (95% CI 1.37 to 5.42, p=0.004) in men whose exercise test duration was less than 8.2 minutes (lowest quartile) as compared with men whose exercise test duration was more than 11.2 minutes (highest quartile) after these adjustments. Additional adjustment for serum triglycerides, HDL and LDL cholesterol, systolic blood pressure, diabetes, fasting serum insulin and plasma fibrinogen had no marked effect on the strength of the associations of VO2max and exercise test duration with overall mortality.

Men in the lowest quartile of VO2max (<27.6 mL/kg/min) had a 3.09-fold (95% CI 1.01 to 9.56, p=0.048) risk of CVD death after adjusting for age, examination year, smoking and alcohol consumption as compared with men in the lowest quartile of VO2max (>37.1 mL/kg/min). Further adjustment for serum triglycerides, serum LDL and HDL cholesterol, systolic blood pressure, diabetes, fasting serum insulin and plasma fibrinogen slightly weakened these associations (p=0.05 for linear trend). A short exercise test duration was related to increased risk of CVD mortality, and the risk of CVD death was 3.44 (95% CI 1.09 to 10.8, p=0.035) times higher among men in the lowest quartile as compared with those in the highest quartile after adjustment for age, examination year, smoking and alcohol consumption (p=0.01 for linear trend). VO2max increase of 3.5 mL/kg per minute (1 MET) was related to a 20% (relative risk, RR 0.80, 95% CI 0.73 to 0.89, p<0.001), 15% (RR 0.85, 95% CI 0.72 to 1.00, p=0.05) and 18% (RR 0.82, 95% CI 0.66 to 0.99, p=0.043) reduced multivariable adjusted risk for all-cause death, CVD and CHD death, respectively.

Furthermore, men in the lowest quartile of VO2max (<27.6 mL/kg/min) had an increased risk of acute coronary events (Figure 1c). After additional adjustment for age, other risk
factors, the use of aspirin and antihypertensive medication and medication for dyslipidemia and exercise-induced myocardial ischemia, the RR of acute coronary events was 2.16 (95% CI 1.12 to 4.12, p=0.021) among men with low VO_{2max}.

![Relative risk](image1a)

**Figure 1a**

Maximal oxygen uptake (mL/kg/min)

![Relative risk](image1b)

**Figure 1b**

Maximal oxygen uptake (mL/kg/min)

**Figure 1.** The age-adjusted risk of overall mortality (a) and CVD death (b) according to the level of VO_{2max} in quartiles (Q). The black bars represent healthy men without CVD and the open bars represent those men with diagnosed disease at baseline. Quartiles in healthy men without CVD: <27.6 (Q1), 27.6-32.2 (Q2), 32.3-37.1 (Q3), >37.1 (Q4, reference group) mL/kg per minute. Quartiles in unhealthy men: <21.2 (Q1), 21.2-27.2 (Q2), 27.3-32.4 (Q3), >32.4 (Q4, reference group) mL/kg per minute. P value for linear trend across the quartiles refers for both healthy and unhealthy men.
5.3.2 Cardiorespiratory fitness, cardiovascular risk factors, all-cause and CVD mortality

VO2max was at least as strong a risk factor as conventional risk predictors for CVD such as high systolic blood pressure (>143 mmHg, highest quartile), obesity (waist-to-hip ratio >0.98, highest quartile), smoking and diabetes. VO2max was inversely related to the risk of death among men with and those without risk factors such as smoking, hypertension, overweight or elevated serum LDL cholesterol. In 1057 men with CVD, pulmonary disease or cancer, VO2max increase of 3.5 mL/kg per minute (1 MET) was related to a 24 % (RR 0.76, 95 % CI 0.70 to 0.82, p<0.001), 29 % (RR 0.71, 95 % CI 0.64 to 0.80, p<0.001) and 28 % (RR 0.72, 95 % CI 0.63 to 0.82, p<0.001) reduced multivariable adjusted risk for all-cause, CVD and CHD death, respectively. The age-adjusted risks of all-cause and CVD death and acute coronary events according to quartiles of VO2max in unhealthy groups are presented in Figures 1(a-c). Multivariable adjusted risks were similar in manner and
magnitude for main outcomes showing a threshold between the lowest and the next lowest group and CVD mortality in unhealthy men. After adjustment for risk factors, the relative risk of CHD death and non-fatal acute coronary events in the lowest quartile of VO_{2max} were 5.84 (95% CI 2.51 to 13.62, p<0.001) and 1.85 (95% CI 1.09 to 3.05, p=0.022), respectively. Lastly, Figure 2 shows risk reduction between VO_{2max} and mortality in men with two combinations of common risk factors among healthy and unhealthy groups.

**Figure 2a.** The multivariable-adjusted relative risks of all-cause death in healthy (a) and unhealthy (b) men classified according to VO_{2max} and according to the number of conventional risk factors (smoking, hypertension and overweight). The risk ratios were adjusted for age, alcohol consumption, diabetes, waist-to-hip ratio, fasting serum insulin, plasma fibrinogen, serum HDL and LDL cholesterol and triglycerides, the use of anti-hypertensive medication, lipid lowering drugs or aspirin and exercise-induced myocardial ischemia. Reference group included most fit men with ≤1 risk factor. Cut-offs were as follows: in healthy groups (a): unfit <27.6, moderate fit 27.6 - 37.1, most fit >37.1 mL/kg per minute, and in unhealthy groups (b): unfit <21.2, moderate fit 21.2 - 32.4, most fit >32.4 mL/kg per minute. ***p<0.001, **p<0.01, *p<0.05.
5.4 Exercise-induced silent myocardial ischemia, coronary morbidity and mortality

5.4.1 Silent myocardial ischemia at baseline and outcomes
There were 189 (10.7 %) men with silent ischemia during exercise and 54 (3.1 %) men with silent ischemia after exercise. Silent ischemia during exercise was observed in 9.6 % of smokers (n=51), in 12.3 % of hypercholesterolemic men (n=110) and in 12.4 % of hypertensive men (n=107). Serum LDL cholesterol, systolic blood pressure and maximal heart rate were higher and BMI was lower in men with silent myocardial ischemia during exercise.

Twenty-nine (15.3 %) out of 189 men with silent ischemia during exercise and 145 (9.2 %) out of 1580 men without silent ischemia had an acute coronary event during follow-up. The respective numbers (percentages) for CHD death were 15 (7.9 %) for men with silent ischemia and 38 (2.4%) in those without myocardial ischemia. Thirteen (7.5 %) out of 54 men with silent ischemia during recovery and 161 (2.6 %) out of 1715 men without silent ischemia had an acute coronary event during follow-up. The respective numbers (percentages) for CHD death were 8 (15.1 %) and 46 (2.7 %).

5.4.2 Silent myocardial ischemia and the risk of acute coronary events and coronary heart disease death
Men with silent ischemia during exercise had a 1.7-fold risk of acute coronary events and a 3.5-fold risk of CHD death as compared with men without silent ischemia after adjusting for conventional risk factors (Table 5). Silent ischemia after exercise was associated with a 2.3-fold risk of acute coronary events and a 4.7-fold risk of CHD death (Table 5). Silent ischemia during exercise and recovery were also statistically significantly associated with increased CVD mortality (Table 5).
Table 5. Risk of acute coronary events, coronary heart disease and cardiovascular disease death according to presence of silent myocardial ischemia in an exercise electrocardiogram in men with no prior coronary heart disease.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Acute coronary events†</th>
<th>CHD death</th>
<th>CVD death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Relative risk (95 % CI*)</td>
<td>P value</td>
<td>Relative risk (95 % CI*)</td>
</tr>
<tr>
<td>Silent myocardial ischemia during exercise‡</td>
<td>1.7 (1.1-2.6)</td>
<td>0.009</td>
<td>3.5 (1.9-6.5)</td>
</tr>
<tr>
<td>Silent myocardial ischemia during recovery‡</td>
<td>2.3 (1.3-4.2)</td>
<td>0.005</td>
<td>4.7 (2.1-10.6)</td>
</tr>
</tbody>
</table>

* CI = confidence interval
† Included 91 definite and 54 possible acute myocardial infarctions and 29 typical chest pain episodes (angina pectoris) of more than 20 minutes leading to hospitalization.
‡ Each variable was entered separately into a Cox multivariable model with age, examination year, cigarette smoking, systolic blood pressure, alcohol consumption, BMI, VO2max, diabetes and serum LDL and HDL cholesterol.

5.4.3 Silent myocardial ischemia, other risk factors and the risk of cardiovascular events

Silent ischemia during exercise had a stronger association with the risk of acute coronary events in smokers, in hypercholesterolemic men and in hypertensive men than in men without such risk factors, after adjustment for age, examination year, cigarette smoking, systolic blood pressure, alcohol consumption, BMI, VO2max, diabetes and serum LDL and HDL cholesterol, except the risk factor of interest (Figure 3a). Silent ischemia during exercise also had a stronger association with the risk of CHD death in these risk groups (Figure 3b). Silent ischemia after exercise had a strong association with the risk of CHD death in smokers (RR 5.0, 95 % CI 2.1-11.9, p<0.001), in hypercholesterolemic men (RR 7.6, 95 % CI 3.0-19.5, p<0.001) and in hypertensive men (RR 6.7, 95 % CI 2.9-16.0, p<0.001) than in men without these risk factors. All of these associations were statistically nonsignificant in men without conventional risk factors, except for nonsmokers with silent
ischemia after exercise who had also an increased risk of CHD death.

**Figure 3a.** The relative risks (95% confidence intervals) of acute coronary events in men with silent myocardial ischemia during exercise according to conventional risk factors levels.

**Figure 3b.** The relative risks (95% confidence intervals) of CHD death in men with silent myocardial ischemia during exercise according to conventional risk factors levels.
5.5 Systolic blood pressure during recovery from exercise and the risk of cardiovascular events

5.5.1 Systolic blood pressure at rest, during and after exercise

Mean maximal systolic blood pressure and systolic blood pressure at 2 minutes after exercise were 202 mmHg and 183 mmHg, respectively. Resting systolic blood pressure had a positive correlation with systolic blood pressure at 2 minutes after exercise ($r=0.53$, $p<0.001$). Diastolic blood pressure at rest had a slightly weaker positive correlation with systolic blood pressure during recovery ($r=0.39$, $p<0.001$). The correlation between maximal systolic blood pressure and systolic blood pressure at recovery was 0.60 ($p<0.001$).

5.5.2 Systolic blood pressure during recovery and acute myocardial infarction

Systolic blood pressure at 2 minutes recovery was a significant predictor for acute myocardial infarction as a continuous variable as well as classified in tertiles. A 10 mm Hg increment in systolic blood pressure at 2 minutes recovery from exercise was related to a 1.07-fold (95% CI 1.03 to 1.12, $p=0.001$) risk of acute myocardial infarction, after adjustment for age, examination year, alcohol consumption, cigarette smoking, serum HDL and LDL cholesterol, serum triglycerides, diabetes, BMI, systolic blood pressure at rest and the use of antihypertensive medications, maximal heart rate, VO$_{2\text{max}}$ and myocardial ischemia during exercise. Furthermore, adjustment for diastolic blood pressure at 2 minutes recovery did not change the observed associations. Systolic blood pressure at 2 minutes recovery was more strongly related to the risk of acute myocardial infarction than diastolic blood pressure at recovery.

Systolic blood pressure of over 195 mmHg at 2 minutes recovery (highest tertile) was related to a 1.7-fold risk of acute myocardial infarction, after adjustment for age, examination year, other risk factors (alcohol consumption, cigarette smoking, serum HDL and LDL cholesterol, serum triglycerides, diabetes, BMI), resting systolic blood pressure, the use of antihypertensive medications, myocardial ischemia during exercise, VO$_{2\text{max}}$ and maximal heart rate (Table 6). If the adjustment was not made by resting systolic blood pressure, the respective risk for acute myocardial infarction remained unchanged.
(RR=1.68, 95% CI 1.27 to 2.21, p<0.001).

Table 6. Relative risks of acute myocardial infarction according to the thirds of systolic blood pressure during 2 min recovery of exercise test.

<table>
<thead>
<tr>
<th>Systolic blood pressure during recovery</th>
<th>Relative risk † (95% CI*)</th>
<th>P value</th>
<th>Relative risk ‡ (95% CI*)</th>
<th>P value</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 170 mmHg (n=816)</td>
<td>1.00 (reference)</td>
<td></td>
<td>1.00 (reference)</td>
<td></td>
<td>99</td>
</tr>
<tr>
<td>170 - 195 mmHg (n=761)</td>
<td>1.17 (0.89-1.55)</td>
<td>0.266</td>
<td>1.30 (0.98-1.72)</td>
<td>0.071</td>
<td>112</td>
</tr>
<tr>
<td>&gt; 195 mmHg (n=781)</td>
<td>1.40 (1.04-1.89)</td>
<td>0.028</td>
<td>1.69 (1.24-2.30)</td>
<td>0.001</td>
<td>147</td>
</tr>
</tbody>
</table>

* CI = confidence interval
† Adjusted for age, examination year, alcohol consumption, cigarette smoking, serum low and high density lipoprotein cholesterol, diabetes, body mass index, resting systolic blood pressure and the use of antihypertensive medications.
‡ Adjusted for age, examination year, alcohol consumption, cigarette smoking, serum low and high density lipoprotein cholesterol, diabetes, body mass index, resting systolic blood pressure, the use of antihypertensive medications, myocardial ischemia during exercise, maximal oxygen uptake and maximal heart rate.

5.5.3 The difference in systolic blood pressure from rest to recovery and acute myocardial infarction

As a continuous variable, a 10 mm Hg increment between the difference in systolic blood pressures measured at rest and 2 minutes after exercise was related to a 1.07-fold (95% CI 1.02 to 1.11, p= 0.011) risk of acute myocardial infarction, after adjustment for age, examination year, other risk factors, resting systolic blood pressure, the use of antihypertensive medications, maximal heart rate, VO$_{2\text{max}}$ and myocardial ischemia during exercise. Men with the largest difference in systolic blood pressure from rest to recovery (>64 mmHg, highest tertile) had a 1.39-fold (95% CI 1.06 to 1.84, p=0.019) adjusted risk of acute myocardial infarction as compared to men with the smallest difference in systolic blood pressure (<44 mmHg, lowest tertile).
5.5.4 Systolic blood pressure during recovery and cardiovascular mortality

Systolic blood pressure during recovery was directly related to the risk of cardiovascular death, after adjustment for age, examination year and other risk factors including systolic blood pressure at rest, the use of antihypertensive medications, maximal heart rate, VO_{2\text{max}} and myocardial ischemia during exercise. Systolic blood pressure after exercise per 10 mmHg increase in the value was related to a 1.06-fold (95 % CI 1.00 to 1.11, p = 0.037) risk of cardiovascular death. Men with high systolic blood pressure (>195 mmHg) during recovery had a 1.45-fold (95 % CI 1.03 to 2.06, p = 0.034) risk of cardiovascular death as compared to men with systolic blood pressure of less than 175 mmHg, after adjustment for age, examination year, other risk factors and exercise test variables.
6. DISCUSSION

6.1 Methodological aspects

6.1.1 Epidemiologic study
Prospective epidemiological studies are placed to show associations between the risk factors of interest and outcome events. In a population based samples of middle-aged individuals, asymptomatic disease may change behaviour and risk factors levels so that the associations are concealed or causation reversed. These factors may cause confounding and lack of independence (123).

The difficulties of measurement and within person variability may minimise true effects. On the other hand, there may be a threshold relationship rather than a linear association between the risk factor and the outcome. In the present study, however, the association between cardiorespiratory fitness and overall mortality was linear, whereas a threshold was observed for the association between cardiorespiratory fitness and CVD mortality among unhealthy men. Secondly, an independent risk factor does not always mean causation. High ranking of a risk factor does not guarantee causation, nor does low ranking indicate a weak relationship. Nevertheless, the strength and independence of the association is an additional evidence for causation. However, it should be realized that an independent predictor has meaning only in the context of a particular statistical model which includes established risk factors (123).

The present prospective population study provides strong evidence that cardiorespiratory fitness, exercise ECG findings and systolic blood pressure during recovery from exercise are associated with the risk of CVD death. This kind of knowledge emphasizes the prevention of CVD in high risk populations as well as at individual level. The CVD epidemic arises from the interaction between a widespread individual susceptibility to disease (i.e. heredity) and environmental risk factors, such as physical inactivity, unhealthy diet and smoking (3, 124, 125). Continued and increased emphasis should be given to the development of prevention skills in clinical practise. This approach enables progress be made in preventive cardiology (125).
6.1.2 Study population

The strength of the present follow-up study is that we have a representative population-based sample of middle-aged men in Finland, the participation rate was high and there were no losses to follow-up. This study provided a valuable opportunity to show the prognostic value of exercise testing in population based sample of men. The study represents a sample of middle-aged male population from eastern Finland, an area known for its high prevalence and incidence of atherosclerotic vascular diseases. The study protocol provided possibility to investigate the predictive value of exercise testing variables in men with different risk profiles. This representative sample of men makes it possible to generalize the observed results in male populations, although the important part of the results on exercise testing and cardiovascular risk should be confirmed in female populations. However, on the basis of some previous studies on women (67, 68, 126), there is no evidence to suggest that the prognostic value of exercise capacity would be different among female subjects. In clinical evaluation, middle-aged and older men include one of the most important target groups that should undergo exercise testing due to their symptoms and medical history suggesting an increased risk of cardiovascular events.

6.1.3 Exercise testing

Cycle and treadmill are two commonly used exercise testing methods. Treadmill exercise is generally the preferred modality in the United States. It is argued that some untrained subjects will terminate cycle exercise because of quadriceps muscle fatigue. However, several studies have demonstrated a consistent relationship between aerobic capacity on treadmill and cycle ergometer (14, 17). Workload increments in exercise test that lead maximal exercise for each person in approximately 10 minutes can be recommended, regardless of the specific protocol or exercise mode. This kind of exercise protocol provides good correlations between observed and predicted oxygen uptake calculated from workloads that increase at constant rate (14).

Cycle ergometer test can be recommended for those who have overweight or joint disorder limiting walking or running because exercise on a cycle is non-weight-bearing whereas walking on the treadmill required good ability to maintain walking balance and
speed (7, 17). Cycle ergometry may be preferred in subjects with balance instability or diseases limiting walking or when simultaneous cardiac imaging and hemodynamic monitoring such as blood pressure is needed. Cycle ergometer tests are usually less expensive, occupy less space, and are less noisy than treadmill tests. Upper body motion is usually reduced, that makes it easier to obtain blood pressure measurements and to record the ECG. Most cycle exercise tests use lower increment in workloads between the stages and thus may be suitable for patients with very low exercise capacity.

The use of direct measure of \( VO_{2\text{max}} \) has the advantage of providing a common assessment of cardiorespiratory fitness for use with different exercise protocols (7, 127). As oxygen consumption is determined primarily by cardiac output in the absence of pulmonary or skeletal limitations, this allows for the use of \( VO_{2\text{max}} \) as an estimate of cardiovascular function during physical stress. As an index of functional capacity, ventilatory gas analysis is the most reproducible measure for scientific research, and peak oxygen uptake is generally more reproducible than exercise time (14). The disadvantages of indirect measures may be that the relationship between oxygen consumption and exercise time is not linear mainly due to large increments in work rate per stage and a wide variety of heterogeneous populations with different basic fitness levels (8). However, in a practical point of view, many large studies estimate the level of cardiorespiratory fitness by the measurements of the duration of exercise, the peak exercise stage, or estimate of the workload achieved during the exercise test. It is well accepted that exercise capacity can be used as an additional noninvasive tool for outcomes providing clinically relevant diagnostic and prognostic information. The direct measurement of the volume of oxygen consumed requires specialized equipment. Thus, many studies estimate cardiorespiratory fitness by the use of indirect assessment of exercise capacity.

One of the strengths of the cycle ergometer test is that it is easy to obtain reliable measurements of blood pressure. The cycle ergometer usually consists of progressive incremental workloads which may have a minor effect on systolic blood pressures achieved between the cycle and the treadmill exercise testing protocols. However, maximal heart rate has been shown to be lower in the cycle ergometer than in the treadmill test, but the rate pressure product to be similar due to a higher blood pressure (128), whereas another study
showed that rate pressure product may be higher during treadmill exercise as compared to cycle exercise (11). It is not plausible that mode of exercise itself may have effect on blood pressure responses during the recovery period after exercise.

Expensive and time-consuming testing methods have not been used in most large population studies. In our study, exercise testing with both conventional indirect definition of exercise capacity as well as respiratory gas analysis is used which is unique in a large population study. Respiratory gases were measured during the exercise test giving us the possibility to explore VO2max as a predictor of premature death in addition to measures of blood pressure and myocardial ischemia by ECG.

6.1.4 The prognostic and diagnostic use of exercise testing
The first reason to estimate prognosis is to provide accurate answers to a subject’s questions about the probable outcome of his or her illness (7). The second reason for determining prognosis is to identify subjects in whom cardiovascular interventions might improve outcome. The predictive value will help to define the diagnostic value of the test. The predictive value of a test is greatly influenced by the prevalence of the disease in the group being tested. The relative risk is useful for providing the physician with an immediate perspective of a patient's overall risk status relative to a low-risk state. This perspective can be helpful as a frame of reference for both the physician and the patient.

The American Heart Association and other organizations have expressed renewed interest in applying screening tests in asymptomatic individuals because of the data showing the ability of the medications to lower cholesterol and to decrease the risk of cardiac events (129). The thought is that a marker of atherosclerosis could help to decide who should or should not be prescribed a statin or other preventive treatment due to their high global risk for CVD. An interest has been focused on the ability of the exercise test to predict risk in asymptomatic cohort (34, 68). Exercise testing provides prognostic information beyond other clinical data (61). Exercise workload was found to be the only exercise testing variable that was strongly associated with cardiovascular outcomes and death although other risk factors were taken into account, and its prognostic effect was of the same magnitude in elderly and younger persons (61). However, it is important to mention that a
good exercise capacity does not rule out the presence of coronary artery disease including single- or multivessel disease (9, 34). On the other hand, most reports suggest that single vessel disease with an obstruction over 70% can be detected by using exercise ECG in about 50 to 60% of men. Thus, we must accept many false-negative responders using the ST segment alone as a risk marker for coronary artery disease.

The exercise test guidelines have not recommended using the standard exercise test for screening mainly due to the problem with false positives in exercise ECG in populations with a low prevalence of CHD (8, 33). There may be poor predictive value in the nonselective use of the test, and invalid abnormal responses (false-positive) may lead to psychological and work disability as well as unnecessary medical expense. Thus, the routine use of the exercise ECG in completely unselected asymptomatic populations cannot be recommended. In asymptomatic men over 45 years old with at least 1 risk factor, exercise testing may provide useful information as a guide to aggressive risk factor intervention or the need to further evaluate the cause of myocardial ischemia (3, 7, 34). Secondly, recent findings support the notion that exercise testing can be used to assess and refine prognosis for CVD, particularly when emphasis is placed also to other measures than exercise ECG (34).

6.1.5 Collection and classification of outcome events

Some studies in asymptomatic subjects have included composite end points and angina pectoris as an outcome. In the current study, main outcome measures were acute myocardial infarction, death from CHD or CVD as well as total mortality, which are considered to be unbiased end points (130). The mortality rate from CHD, and particularly the total mortality rate, may be less subject to ascertainment bias than is the total number of CHD events or composite end points and hence may be more valid measures. It is suggested that death from any causes can be considered a truly unbiased and objective end point (130, 131). Hard end points, such as death, eliminate the risk of misclassification and are appropriate for classifying cardiovascular risk.

During the follow-up, it is possible to assess both cause-specific mortality and overall mortality as hard end points. The study is based on reliable data on outcome events because
deaths were ascertained from the Finnish National Death Registry using personal identification codes. Data on coronary events were obtained by computer linkage to the national hospital discharge and death registers. The source of this information was checked by interviews, hospital documents, death certificates, autopsy reports and medico-legal reports. The diagnosis of acute coronary event is typically based on symptoms, ECG and cardiac enzymes or autopsy findings.

6.2 Cardiorespiratory fitness and cardiovascular mortality

Blair and co-workers (54, 65) found that moderate levels of cardiorespiratory fitness defined by quintiles of treadmill test time were associated with reduced all-cause and cardiovascular mortality, while higher levels provided only little further reduction in the risk of death. This finding is supported in the study by Myers and co-workers (60) showing that the greatest risk reduction was between the least fit and the next fit quintiles. Sandvik and co-workers (57) observed that moderate levels (quartiles) of work capacity in bicycle ergometer test were associated with reduced cardiovascular mortality, but there was some further reduction in the risk at the highest levels. However, Ekelund and co-workers (55) showed a marked difference in cardiovascular mortality between high and low levels of cardiorespiratory fitness assessed by heart rate at a speed of 4 km/h (2.5 miles/h) on a treadmill. Thus, these observations concurs with the consensus (132, 133) that the greatest health benefits are achieved by increasing physical activity among the least fit subjects.

A clinically important finding is that the inverse associations were observed within categories of common risk factors including smoking, elevated blood pressure, serum cholesterol and body mass emphasizing the protective effect of good cardiorespiratory fitness among individuals with or without the presence of other risk factors (65). It is also reported that peak exercise capacity was a more powerful predictor than many other common clinical and exercise test variables (60). Good exercise capacity was a strong predictor of mortality in men with history of hypertension, chronic obstructive pulmonary disease, diabetes, smoking, obesity or elevated serum total cholesterol level as well as in subjects with or without underlying cardiovascular disease or the use of β-blockers (60).
Integration of exercise capacity and conventional risk factors improved CHD risk assessment substantially, especially among smokers with high cholesterol levels (134). It is suggested that exercise test when combined with the global risk score may be useful for risk stratifying in asymptomatic individuals in a comprehensive executive health screening program (135). It may be reasonable to limit such referrals to those with a higher global risk scores (135).

The expert panel suggested that every adult should accumulate 30 minutes or more of moderate-intensity physical activity on most, preferably all, days of the week to promote health and to prevent chronic diseases (132, 133). In a randomized trial (136), the authors estimated that an increase of 10% in cardiorespiratory fitness, corresponding to 1 MET increase in exercise capacity, can be achieved by maintaining these exercise recommendations for 2 years. However, more intense structured exercise could increase physical fitness by 1 MET in 6 months (136). Blair and co-workers (65) reported that an increase of 2 METs in treadmill exercise capacity was related to a reduction of 30% in age-adjusted mortality. In a large study, Myers and co-workers (60) reported a nearly linear reduction in mortality as fitness levels increased, and each increase of 1 MET in exercise capacity conferred a 12% improvement in survival among men referred exercise testing for clinical reasons. Comparable risk reduction in each 1 MET increment in workload was found among younger and older subjects (61). Previous studies have suggested that even a small improvement in cardiorespiratory fitness and an increase in physical activity can result in reduced all-cause and cardiovascular mortality (56, 62, 64).

This prospective population-based study among middle-aged men from Eastern Finland, that used VO2max and exercise test duration through their whole ranges as measure of cardiorespiartory fitness, showed strong, graded and inverse associations with overall and cardiovascular mortality. In fact, VO2max and exercise test duration were one of the strongest predictors for mortality in the present unselected middle-aged male cohort. The mortality curves for the quartiles of VO2max continued to diverge over the period of follow-up and the strongest excess mortality was found at low levels of VO2max. Furthermore, the present study showed that good VO2max reduces the risk of premature death among healthy men and subjects with an unfavourable risk profile or known CVD. These findings support
U.S. cohort studies (60, 65, 69) suggesting that the risk of death associated with low cardiorespiratory fitness is comparable with that of conventional risk factors including smoking, hypertension, hypercholesterolemia, obesity and diabetes.

Cardiorespiratory fitness has a heritable and an acquired component from aerobic exercise training. Both components show considerably heterogeneity presumably related to an integration between genetic and environmental factors (21). Further, individual responses of VO2max to exercise training are extremely variable because of a strong genetic contribution (21, 22). The optimal intensity of exercise and the level of cardiorespiratory fitness recommended for the subjects with atherosclerotic diseases should be defined individually in different risk groups that exercise can be used as a safe treatment. The conclusion that clinicians should always encourage their patients to increase cardiorespiratory fitness may lead to unwanted consequences such as sudden cardiac death if previous training history is not defined (137).

Accumulating evidence from controlled randomized trials emphasizes that many improvements in health related fitness can be achieved by even low intensity exercise, that may not always increase exercise performance (Figure 4) (138). The curve A may be described as the dose-response pattern upon which the current recommendations for physical activity are based as well as how some benefits for cardiovascular risk factors can be achieved. The second pattern represents a linear relationship (Curve B), which most likely represents the relationship between cardiorespiratory fitness and cardiovascular events. However, some other benefits can be achieved only at high levels of physical activity (Curve C), especially if the initial physical fitness level is high.
Figure 4. Schematic illustration (three different associations) depicting the relationship between physical activity level defined in energy expended and health effects (see text for explanation).

An increasing amount of previous data from follow-up studies supports the measurement of cardiorespiratory fitness in clinical practice. Our results suggest that middle-aged men without cardiovascular or pulmonary disease but who have exercise capacity below 7-8 METs have an increased risk of premature death. Among those with previous CVD, the risk of death was markedly increased if exercise capacity was below 5 METs. In addition to abnormal exercise ECG findings and blood pressure changes, low levels of cardiorespiratory fitness should be taken into account when the future risk of death is estimated among patients undergoing exercise test.

6.3 Silent myocardial ischemia and the risk of coronary heart disease

Prognosis has been studied by a variety of investigators who have documented silent myocardial ischemia with use of exercise ECG, exercise radionuclide procedures or ambulatory ECG monitoring (38). There is a general agreement that the presence of
ischemia itself rather than associated angina pectoris worsens prognosis.

Unrecognized myocardial ischemia is a common finding and increases the risk of future coronary events (40, 139). We observed that painless ST depression during exercise was present in almost 11% of the men. In general, the prevalence of an abnormal exercise ECG result has varied from 5 to 12% in asymptomatic men (140, 141). Among diabetic patients, however, silent ischemia was present in 13.5% of those undergoing exercise testing (141). In daily life, ischemic ST depression in the absence of pain has been more common than ST depression with angina (139, 142, 143). Exercise testing in asymptomatic population is controversial because of the high false positive rate in such individuals (30). In men from eastern Finland, the prevalence of atherosclerotic CVDs was one of the highest in the world at the initiation of the follow-up study. This observation suggests at least moderate sensitivity of exercise test, although typical symptoms for CHD were not present.

In the current study, the coexistence of at least one conventional risk factor in addition to ST depression substantially increased the risk of acute coronary events and death from CHD. The guidelines from the American Heart Association and the American College of Cardiology suggest that there is weak supportive evidence to evaluate asymptomatic persons with multiple risk factors (hypertension, hypercholesterolemia, smoking, diabetes, family history of CHD) or those who are at high risk for CHD due to other atherosclerotic diseases (7, 8). Some studies have shown that the more frequent or progressive the anginal symptoms, the poorer is the prognosis in patients with CHD (86, 88, 144). Other studies have indicated that symptomatic and silent ischemia are related to a similar prognosis in patients with symptomatic (87, 89, 90) and mildly symptomatic (89) CHD. As patients become selected towards a higher a priori likelihood of developing myocardial ischemia and CHD, there appears to be a tendency for chest pain to lose its significance as an additional predictive factor (144).

The prognostic value of silent myocardial ischemia, as indicated by exercise ECG findings, varies considerably in the published reports (39, 86, 91, 145), most likely due to different selection criteria for the subjects. Most studies have included only patients with CHD (87, 89, 90), whereas few studies have included persons without prior CHD (39). It has been argued that the prognostic value of exercise ECG is low in totally asymptomatic
persons because of false positive and false negative responders. However, in healthy individuals with a high pre-test probability of CHD, i.e. in those with major coronary risk factors, the frequency of false positive test responses for myocardial ischemia is lower than in those without coronary risk factors, which diminishes the bias associated with false-positive responders (3, 91). This could be one explanation for our finding that the association between silent myocardial ischemia with coronary risk was stronger in high risk groups.

The suboptimal sensitivity of ST-segment response for predicting CHD events may be explained in part by the fact that ST-segment depression on exercise testing detects ischemia from obstructed coronary arteries, but many acute coronary events results from sudden occlusion of a previously nonobstructed segment of artery (34, 146). The sensitivity of exercise testing to detect myocardial ischemia may be further improved by ECG recordings not only during exercise but also after exercise. However, very few studies have provided evidence that ischemic ST depression after exercise would have an adverse prognostic value with regard to coronary events in apparently healthy men (147, 148). In the present study, silent myocardial ischemia during recovery was even a stronger predictor of future events than silent myocardial ischemia during exercise, especially with regard to CHD death. This suggests that silent myocardial ischemia during post-exercise period could be of great clinical importance, and the prognostic value of exercise testing can be improved by assessing ischemic ECG changes during recovery.

Some previous studies have suggested that silent myocardial ischemia is a pathophysiological mechanism through which exercise increases the occurrence of sudden death (143, 144, 149). One explanation for this could be that painless ischemia increases the susceptibility to myocardial infarction, left ventricle dysfunction and ultimately fatal ventricular arrhythmias. The transient impairment of coronary flow during and after exercise may be caused by dynamic coronary stenosis as a result of epicardial coronary constriction, endothelial dysfunction, spasm and thrombosis (142, 143). Such brief episodes may be painless because the stimulus is either inadequate or the pain usually appears quite late after the onset of ischemia (40, 144). One mechanism for silent myocardial ischemia after exercise is the rapid decline in diastolic blood pressure during recovery, which
reduces the myocardial perfusion pressure gradient and transiently impairs subendocardial blood flow (148). Exercise-induced ischemic preconditioning of the myocardium may reduce the amount of myocardial damage and the risk of fatal ventricular arrhythmias upon a subsequent coronary occlusion and prolonged ischemia.

Comparable hemodynamic and wall-motion abnormalities indicative of ischemia were observed in patients with and without angina (150). A possible role of endorphin related pain response also has been studied. However, this issue is not clear, as different laboratories that have measured plasma endorphin levels during and after exercise tests have produced conflicting results (87). Holter monitoring has proven useful in clarifying pathophysiologic mechanisms during silent ischemia. Some studies have noted that a large amount (almost 80 %) of total ischemic episodes were silent and the most of the asymptomatic episodes were short (40). It is apparent that there is circadian variation in ischemic episodes, with most coming after arousal in morning, or waking and rising at night (38). This pattern seems to be similar for heart rate, plasma catecholamines, platelet aggregability, arterial blood pressure, and tone in epicardial arteries.

6.4 Systolic blood pressure during recovery from exercise and the risk of coronary heart disease

It has been previously suggested that abnormal systolic blood pressure response is an important indicator for coronary artery disease not only during exercise but also during the recovery phase (113, 151, 152). Some studies observed that an abnormal ratio of recovery to peak exercise was even more sensitive than exercise-induced angina or ischemic ECG changes for diagnosing the severity of CHD (113, 152). In patients with angina pectoris, an abnormally high systolic blood pressure response during recovery was very sensitive for the diagnosis of multivessel CHD suggesting the close correlation between this response and the severity of CHD (151).

Consistent with a previous study showing the role of delayed slowing of heart rate (28), elevated systolic blood pressure immediately after exercise may also reflect the overactivity of sympathetic nervous system and attenuated vagal reactivation. During graded exercise,
the heart rate and systolic blood pressure progressively increases, owing to an increase in activity of the sympathetic nervous system with a concomitant decrease in the parasympathetic activity (153). Autonomic dysfunction and vasoreactivity abnormalities may account for the gradual decrease of systolic blood pressure after exercise (48, 96). Furthermore, the structural adaptations of the cardiovascular function serve to maintain higher systolic blood pressure levels and contribute to a structurally induced hyperreactivity with no decrease in vascular resistance (48). An attenuated decrease in exercise blood pressure also may be due to poor arterial compliance in individuals with underlying vascular smooth muscle hypertrophy and subclinical arteriosclerotic changes (154). High blood pressure during recovery from exercise probably also responds with an increase in peripheral resistance.

It is also possible that a high preload continues during recovery in patients with myocardial ischemia and a high risk for acute myocardial infarction. An abnormal systolic blood pressure response may be caused from recovery of myocardial ischemia and an increase in systemic vascular resistance secondary to exaggerated sympathetic nervous activity. Both norepinephrine and epinephrine levels have been found to increase in response to exercise, and both levels have been shown to increase continuously immediately after exercise (155). It is biologically plausible that repeated sympathetic activation in the absence of metabolic need leads to systolic blood pressure elevations beyond the normotensive range. Sympathetic activation during the anticipation phase of exercise is manifested as an increase in cardiac output with no compensatory decrease in vascular resistance (120).

Potential mechanisms by which an exaggerated rise in exercise blood pressure could cause exercise-induced ischemic ECG changes may be an excessive rate-pressure product that could result in global subendocardial ischemia due to a mismatch between myocardial oxygen supply and demand (156-158). Exercise-induced myocardial ischemia occurs commonly and coronary vasodilator reserve is reduced in patients with left ventricle hypertrophy and elevated systolic blood pressure (103). Thus, myocardial ischemia can occur in hypertensive patients due to abnormally elevated resistance at the coronary microvascular level (103). This kind of mechanism may also occur in patients who are
normotensive at rest but hypertensive during exercise as well as immediately after exercise. Abnormal loading conditions can cause ischemic ST changes in ECG changes that are interpreted false positive which is supported by the finding that asymptomatic adults can develop ST-segment depression and abnormal left ventricular contractility by performing sudden vigorous exercise (159).

This study with blood pressure recordings during cycle exercise test shows that systolic blood pressure during the recovery period may provide an additional risk marker for identifying individuals at an increased risk for acute myocardial infarction. Systolic blood pressure response after the progressive cycle exercise can be considered as a risk predictor for acute myocardial infarction. Thus, the measurement of systolic blood pressure immediately after exercise test provides supplementary information for the risk of acute myocardial infarction by comparison with resting blood pressure.
7. SUMMARY AND CONCLUSIONS

1. Cardiorespiratory fitness represents one of the strongest predictors of mortality emphasizing the importance of exercise testing in clinical practise. Cardiorespiratory fitness provides valuable additional information with the presence of other risk factors, and can be considered to be at least as strong a risk factor as smoking, dyslipidemia, hypertension, diabetes and obesity.

2. Cardiorespiratory fitness provides a valuable tool for prognostic assessment. Regardless of the population being healthy or unhealthy and despite the many advances in cardiac imaging, the assessment of exercise capacity remains an important tool for the prediction of CVD. If exercise capacity is poor, prognosis seems to be poor although ECG changes and other risk factors are taken into account.

3. Silent myocardial ischemia during exercise and recovery, as indicated by ST depression in ECG, predicts acute coronary events and CHD death. Painless myocardial ischemia is of significant additional prognostic value when any conventional risk factors are present in men clinically free of CHD. Exercise-induced silent myocardial ischemia appears to be a stronger predictor of CHD in men with an unfavourable coronary risk profile. The present study emphasizes the importance of exercise testing in identifying high risk persons who would most likely benefit of preventive measures.

4. Careful assessment of systolic blood pressure and ECG during recovery from exercise provides important prognostic information. Systolic blood pressure responses during an exercise test provide additional risk markers for identifying individuals at an increased risk for future cardiovascular events.
8. REFERENCES


136. Dunn AL, Marcus BH, Kampert JB, Garcia ME, Kohl HW, 3rd, Blair SN. Comparison of lifestyle and structured interventions to increase physical activity and cardiorespiratory fitness: a randomized trial. JAMA 1999;281:327-34.


ORIGINAL PUBLICATIONS


Original publications have been reproduced with the permissions from the American Medical Association (I), Oxford University Press (II), Elsevier Science Inc. (III) and Lippincott, Williams & Wilkins (IV).


