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Exercise Stress Test in Stroke Risk Prediction

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ABSTRACT

Exercise testing is a widely accepted diagnostic testing method. Previous studies have shown that physical fitness is one of the strongest risk factor for cardiovascular diseases (CVDs). Systolic blood pressure (SBP) during exercise test is an important hemodynamic variable. However, the prognostic value of systolic blood pressure during and after exercise test is not known with respect to stroke. Both exercise-induced painful and painless ischemia have been previously documented as risk predictors for ischemic cardiac events. But little is known about silent ischemia during exercise test and the risk of stroke. Systolic blood pressure, exercise-induced myocardial ischemia and cardiorespiratory fitness were assessed using a maximal, symptom-limited exercise test on an electrically braked cycle ergometer. Respiratory-gas exchange was measured for the 2361 men in a population based sample of men. During the follow-up, the classification of stroke events was carried out according to the multinational MONICA project.

Men with SBP rise >19.7 mm Hg per minute of exercise duration had a 2.3-fold increased risk of any stroke and a 2.3-fold increased risk of ischemic stroke compared with men whose SBP rise was <16.1 mm Hg/min. Similarly, percent maximum SBP at 2 minutes after exercise (SBP at 2 minutes' recovery divided by maximum SBP) was associated (highest tertile) with a 4.6-fold increased risk of any stroke and a 5.2-fold increased risk of ischemic stroke.

The relative risk for any stroke in unfit men (VO_2max, <25.2 mL/kg per minute) was 3.2 (95% CI, 1.71-6.12); and for ischemic stroke, 3.50 (95% CI, 1.66-7.41), compared with fit men (VO_2max, >35.3 mL/kg per minute), after adjusting for age and examination year.

Thirdly, men with silent ischemia during exercise had a 2.2-fold increased risk of stroke compared with men without silent ischemia, after adjusting for conventional risk factors. Silent ischemia during exercise was associated with a 3.8-fold (95% CI, 1.1 to 12.5) increased risk for stroke in smokers, a 3.5-fold (95% CI, 1.7 to 7.4) increased risk in hypercholesterolemic subjects, a 3.4-fold (95% CI, 1.6 to 7.1) increased risk in the hypertensives, and 2.9-fold (95% CI, 1.4 to 6.1) increased risk in overweight men.

Men with low exercise cardiac power (<10.3 mL/mm Hg) had 2.7-fold (95% CI, 1.2 to 6.0; P=0.01), risk for stroke and 2.7-fold (95% CI, 1.1 to 7.0; P=0.03) risk for ischemic stroke compared with men having high exercise cardiac power during exercise after adjusting for conventional risk factors. Cardiorespiratory fitness provides additional valuable prognostic information with the presence of other risk factors, and can be considered to be at least as important a risk factor as smoking, dyslipidemia,

hypertension, type II diabetes and obesity. Silent myocardial ischemia during exercise testing predicts not only acute coronary events but also stroke in men with various risk factors. The clinical implication of this study is that painless myocardial ischemia is of strong prognostic value in the presence of conventional risk factors in men free of CHD, thereby stressing the importance of identifying high risk persons with exercise testing who are in the need of preventive measures. Systolic blood pressure responses during an exercise test can be used for identifying individuals at an increased risk for stroke.

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Medical Subject Headings: Exercise Test; Ergometry; Stroke; Cardiovascular Diseases; Risk Factors; Blood Pressure; Myocardial Ischemia; Physical Fitness; Smoking; Hypercholesterolemia; Hypertension; Overweight

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TIIVISTELMÄ

Huono fyysinen kunto ja vähäinen liikunta-aktiivisuus ovat nykyisen tutkimustiedon perusteella sydän- ja verisuonisairauksien riskitekijöitä. Epidemiologisissa tutkimuksissa huono fyysinen kunto on todettu jopa yhtä tärkeäksi sydän- ja verisuonisairauksien riksiä ennustavaksi tekijäksi kuin tupakointi, korkea kolesteroli, kohonnut verenpaine, tyypin II diabetes ja ylipaino.

Tässä itä-suomalaisessa väestöpohjaisessa seurantatutkimuksessa fyysinen suorituskyky, sydänlihasiskemia ja verenpaine mitattiin maksimaalisen rasituskokeen aikana 2361 mieheltä. Suorituskyky määritettiin kuormituskokeen aikana myös suoralla menetelmällä hengityskaasujen perusteella. Tutkimuksessa selvitettiin keskeisten kuormituskoelöydösten ennusteellista merkitystä, ja seurattavat päätetahtumat olivat aivohalvaus sekä kuolleisuus muihin sydän- ja verenkiertoelinsairauksiin. Aivohalvaukset luokiteltiin sairaalapoistotietojen ja valtakunnallisen kuolinsyyrekisterin tietoihin perustuen.

Tutkimuksen keskeisenä löydöksenä oli se, että suoralla menetelmällä mitattu maksimaalinen hapenkulutus ennustaa aivohalvauksen ja iskeeminen aivohalvaus riskiä sekä oireettomilla henkilöillä että niillä joilla on jo tiedossa oleva oireinen sydänsairaus tai muita perinteisiä riskitekijöitä. Tämä tutkimus osoittaa myös sen, että kivuton iskeeminen EKG muutos fyysisen kuormituksen aikana ennustaa aivohalvauksen riskiä erityisesti sellaisilla miehillä, joilla on riskitekijöinä tupakointi, korkea verenpaine tai kohonnut veren kolesterolitaso. Sen sijaan sellaisilla henkilöillä joilla ei ole perinteisiä sepelvaltimotaudin riskitekijöitä, kivuttomalla iskeemisellä rasitus EKG muutoksella ei ollut itsenäistä ennusteellista merkitystä. Tutkimuksessa todettiin myös se, että kuormituskokeen aikana mitattu korkea verenpaine on aivohalvauksen riskitekijä. Erityisesti korkea systolinen verenpaine maksimaalisen rasituksen jälkeisessä palautumisvaiheessa ennusti aivohalvauksen riskiä. Maksimaalisen hyperkulutuksen ja verenpaine suhde rasituskokeessa on myos vahva aivohalvauksen riskin ennustaja.

Tämä väestötutkimus antaa uutta tietoa kliinisen kuormituskokeen merkitystä riskiryhmien ennusteen arvioinnissa. Fyysinen suorituskyky on tärkeä ennusteellinen tekijä kuormituskokeessa todettujen iskeemisten EKG muutosten sekä systolisen verenpaineen muutosten ohella. Kuormituskoelöydöksillä on ennusteellista lisäarvoa perinteisiin riskitekijöihin nähden. Kuormituskokeen tulosten perusteella voidaan antaa tutkittaville tietoa sydänsairauden riskistä, lisäksi aivohalvauksen hoidon tarpeesta sekä edelleen motivoida aivohalvauksen ennaltaehkäiseviin toimenpiteisiin.

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Luokitus: WG 141.5F9, WL 356, WG 106, WG 120, QT 255
Yleinen suomalainen asiasanasto: rasituskokeet; aivohalvaus; sydän- ja verisuonitaudit;
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LIST OF ORIGINAL PUBLICATIONS

This dissertation is based on the following original publications:

I   Kurl S, Laukkanen JA, Rauramaa R, Lakka TA, Sivenius J, Salonen JT. Systolic blood pressure response to exercise stress test and the risk of stroke. Stroke 2001; 32:2036 -2041.

II   Kurl S, Laukkanen JA, Tuomainen TP, Rauramaa R, Lakka TA, Salonen R, Eränen J, Sivenius J, Salonen JT. The association exercise induced silent ST depression with the risk of stroke and cardiovascular diseases in men. Stroke 2003;34: 1760 -1765.

III   Kurl S, Laukkanen JA, Rauramaa R, Lakka TA, Sivenius J, Salonen JT. Cardiorespiratory fitness and the risk of stroke in men. Arch Intern Med 2003: 163:1682 -1688.

IV   Kurl S, Laukkanen JA, Niskanen L, Rauramaa R, Tuomainen TP, Sivenius J, Salonen JT. Cardiac power during exercise and the risk of stroke in men. Stroke 2005; 34: 1760-1765.

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CONTENTS

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ABBREVIATIONS

BMI	**Body mass index**
CHD	**Coronary heart disease**
CVD	**Cardiovascular disease**
CI	**Confidence interval**
DBP	**Diastolic blood pressure**
ECG	**Electrocardiogram**
HDL	**High density lipoprotein**
ICD	**International classification of disease**
KIHD	**Kuopio Ischemic Heart Disease Risk Factor Study**
LDL	**Low density lipoprotein**
L	**Liter**
METs	**Metabolic equivalents**
MONICA	**MONItoring of Trends and Determinants in CArdiovascular Disease**
SBP	**Systolic blood pressure**
VO$_{2max}$	**Maximal oxygen uptake**

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1 Introduction

Stroke is the leading cause of morbidity and and the third-leading cause of mortality after ischaemic heart disease and cancer. Stroke remains a major healthcare problem, and it is the most common neurological reason for hospitalization. Although we have made great strides in the diagnosis and treatment of stroke, the overall incidence of stroke will continue to rise as our population ages. Primary prevention of stroke is of vital importance because over 70% of the strokes are first events. It is estimated that there are over 700,000 and 14,000 incident strokes in the United States and Finland each year respectively (American Heart Association, Heart Disease and Stroke Statistics-2004 Update, Sivenius J, et al 2009). A major reason for the decline in stroke incidence and mortality during the last two decades is the general reduction in risk factors and the development of preventive therapies. Secondly, there has been the awareness and favourable control of various cardiovascular risk factors.

Stroke is a leading cause of functional impairments, with 20% of survivors requiring institutional care after 3 months and approximately 15% to 30% being permanently disabled.

The main aim of the current study was to identify variables derived from exercise stress test which may serve as useful predictors for future stroke events and possibly provide additional prognostic information to conventional risk factors in a population-based sample of middle-aged men.

2 Review of Literature

2.1 Stroke

"Stroke" as a term is non-spesific, comprising of a herterogenous group of distinct patho-physiologic causes, including thrombosis, embolism and hemorrhage. It is also the most common neurological reason for hospitalization. Although, we have made great strides in the diagnosis and treatment of stroke, the overall incidence of stroke will continue to rise as our population ages. The etiology of stroke is that it is a heterogeneous disease with three main pathological subtypes: ischaemic stroke, intracerebral haemorrhage, and subarachnoid haemorrhage. Ischaemic stroke is further classified into different subtypes according to clinical syndromes and the presence of cardiac sources of embolism, atherosclerotic arterial disease, disease of small penetrating arteries, or various rarer causes. The prognosis and treatment differ according to the subtype. Ischaemic stroke is the most common cerebrovascular disease which is due to the underlying atherosclerosis. Stroke has both non-modifiable and modifiable risk factors.

2.1.1 Definition of Stroke

Stroke is defined as a sudden loss of brain function caused by a blockage or rupture of a blood vessel to the brain. The symptoms last for more than 24 hours. Stroke can be subdivided into two types: ischemic and haemorrhagic. Ischaemic stroke accounts for 75-85% of all cases. Haeorrhagic stroke can be further sub-classified as intra-cerebral and sub-arachnoid.

2.1.2 Ischaemic Stroke

Ischemic stroke is classified according to the etiological mechanisms into five different diagnostic subgroups: large-artery atherosclerosis, cardioembolism,

smale-vessel-vessel occlusion, stroke of known or determined etiology and stroke of other undetermined etiology. In ischemic stroke, an interruption of the blood supply to the brain results in tissue hypo-perfusion, hypoxia, and eventual cell death secondary to a failure of energy production. In atherothrombotic disease, lipid deposition leads to the formation of plaque, which narrows the vessel lumen and results in turbulent blood flow at the area of stenosis. The turbulence of the flow and the resultant changes in blood flow velocities lead to intimal disruption or plaque rupture, which activate the clotting cascade. This in turn leads to activation of platelets and adhere to the plaque surface, where they eventually form a fibrin clot. As the lumen of the blood vessel becomes more occluded, ischemia develops distal to the obstruction and can eventually lead to an infarction of the tissue that is dependent on the parent vessel for oxygen delivery.

2.1.3 Embolic Disease

Embolic stroke occurs when dislodged thrombi travel distally and occlude vessels downstream. All most 50 percent of all embolic strokes are caused by atrial fibrillation; the rest are attributable to a variety of causes, including (1) left ventricular dysfunction secondary to acute myocardial infarction or severe congestive heart failure, (2) paradoxical emboli secondary to a patent foramen ovale, and (3) atheroemboli. These latter vessel-to-vessel emboli often arise from atherosclerotic lesions in the aortic arch, carotid arteries, and vertebral arteries.

2.1.4 Haemorrhagic Stroke

Intracerebral haemorrhage is the result of the rupture of a vessel within the brain parenchyma. The primary causes of these ruptures are hypertension and amyloid angiopathy. As with ischemic stroke, the location of an

intracerebral haemorrhage determines the type of symptoms and the patient's overall outcome. For example, a small lobar haemorrhage might cause only a mild headache and subtle motor deficits, while a haemorrhage of the same size in the pons might result in a coma. Outcomes are also correlated with the volume of blood; haemorrhages greater than 60 ml are almost always fatal, regardless of their location.

2.2 Stroke and risk factors

2.2.1 Risk factors for stroke

Cerebral and cardiac atherosclerosis share many pathogenic mechanisms and risk factors. Studies provide convincing evidence that cardiac events occur more often in patients with cerebral disease. Hence it is important for risk factor assessment to determine the therapeutic strategy, because the intensity of preventive intervention is tailored to the patient's risk of coronary heart disease (Sivenius J, et al 2009). The most important risk factors for stroke include age, hypertension, smoking, diabetes, obesity, physical inactivity, alcohol consumption, cardiac co-morbidity, particularly atrial fibrillation, elevated serum total cholesterol and low-density lipoprotein (LDL) cholesterol and low high-density lipoprotein (HDL) cholesterol, as well as menopausal status in women. Aggressive risk factor reduction, also used in secondary prevention, may be vital to optimal patient management in primary prevention (Sivenius J, et al 20092, Lewington S, et al 2002).

Risk factors for stroke are either modifiable or non-modifiable. Among the latter are age, sex, race/ethnicity, and family history. Beginning at the age of 55 years, the incidence of stroke doubles every decade. Men are more likely than women to experience early stroke (prior to age 65 yr) and carotid artery stenosis. The modifiable risk factors for stroke include hypertension, diabetes,

cigarette smoking, hyperlipidemia, carotid artery stenosis, atrial fibrillation, excessive alcohol consumption, and physical inactivity.

2.2.2 Hypertension

The most important modifiable risk factor is hypertension, which increases the risk of stroke from 2- to 4-fold (Vasan RS et al 2002, Chobanian AV et al 2003, Collins R et al 1990). Higher the blood pressure, greater is the risk of stroke. Blood pressure particularly systolic blood pressure (SBP) increases with increasing age. This higher risk is seen in both systolic and diastolic hypertension as well as in isolated systolic hypertension in the elderly. The Framingham Study observed that individuals who are normotensive at 55 years of age have a 90% lifetime risk for developing hypertension (Kannel WB et al, 1981, Vasan RS et al 2002). Blood pressure control significantly reduces the risk of stroke; it has been shown to prevent 30 strokes for every 1000 patients treated. Recent guidelines recommend lowering blood pressure to less than 140/90 mm Hg ((Goldstein LB et al 2001), with lower targets in subgroups, such as subjects with diabetes.

2.2.3 Diabetes

Individuals with type 2 diabetes have both an increased susceptibility to atherosclerosis and an increased prevalence of atherogenic risk factors mainly hypertension, obesity and dyslipidemia. Type 2 diabetes increases stroke risk from 1.8- to 6-fold (Kannel WB et al 1979). Although there is no clear evidence that normalizing blood glucose values itself specifically reduces the stroke risk, the Stroke Council's guidelines clearly state that hyperglycemia should be controlled to reduce the risk of microvascular complications (Goldstein LB et al 2001).

2.2.4 Smoking

Most of the studies have identified cigarette smoking as a potent risk factor for stroke. Smoking increases the risk for ischemic stroke as well as hemorrhagic stroke (Kawachi I, et al 1993, Wolf PA, et al 1988, Wannamethee SG et al 1995). There is growing evidence to show that exposure to passive smoking is a risk factor for stroke with the risk approaching the doubling found for active smoking. Smokers have a relative risk of stroke in the range of 2-fold, and the estimated population atributable risk of stroke due to smoking is 18%. Smoking a single cigarette increases heart rate, mean blood pressure and cardiac output and also decreases arterial distensibility. The most important preventive measure is smoking cessation and minimizing the exposure to passive smoking.

2.2.5 Hyperlipidemia

Epidemiological studies have found inconsistent association between cholesterol levels and overall stroke rates. This can be due to the likely confounding by the inclusion of ischemic as well as hemorrhagic strokes. Dyslipidemia has been shown to increase the risk of stroke by 1.8- to 2.6-fold (Iso H et al 1989, Lancet 1995). Most of the information regarding the effect of lowering cholesterol on stroke risk comes from secondary analyses of trials on the prevention of coronary disease, but it is prudent to use these guidelines when evaluating patients for stroke risk. Tighter control of hyperlipidemia is indicated for patients who have a history of stroke or cardiovascular disease; the goal LDL level is less than 2.8 mmol/L, their target HDL level is greater than 1.0 mmol/L, and their recommended total cholesterol level is less than 5.0 mmol/L.

2.2.6 Alcohol consumption

Heavy drinking and binge drinking are related to an increased risk of both ischemic and hemorrhagic stroke (Gill JS et al 1986, Berger K et al 1999, Stampfer MJ et al 1988). But light and moderate drinking is known to decrease the risk of stroke compared to non-drinking. The majority of studies have suggested a J-shaped relationship between alcohol consumption and ischemic stroke with abstainers and heavy drinkers having a higher risk than light drinkers. The risk of hemorrhagic stroke seems to increase steeply with increase in alcohol consumption. This association between alcohol consumption and the risk of stroke has been suggested to be mediated by HDL cholesterol, blood pressure, platelet aggregration and fibrinolytic activity. Moreover heavy alcohol consumption can lead to hypertension, reduced cerebral blood flow and greater likelihood of atrial fibrillation.

2.2.7 Obesity

A growing body of evidence from large prospective studies has documented that increased body weight is associated with an increased risk of stroke in a dose-response fashion (Kurth T et al2002, Rexrode KM et al 1997, Suk SH et al 2003). Obesity has been identified as an independent risk predictor for stroke. In Framingham cohort a relative weight of 30% above the average age was associated with an increased risk of stroke in men 35 to 64 years of age (Hubert HB et al 1983). The prevalence of obesity and overweight has been increasing everywhere in the world. Obesity has been associated with elevated blood pressure, blood glucose and serum lipids.

2.2.8 Physical activity

Regular physical activity has well-established benefits for reducing the risk of premature death and cardiovascular diseases Lee IM, et al 1999, Hu FB et al

2000, Pate RR et al 1995). Physical activity is known has been inversely related to the risk of stroke, although the relation has been inconsistent. The association has been either a graded dose-response relation or a nonlinear association between physical activity and the risk for stroke mainly by affecting modifiable risk factors, including hypertension, obesity, diabetes. Other biological mechanisms have also been associated with physical activity including reductions in plasma fibrinogen, platelet aggregation and elevations in plasma tissue plasminogen activator activity and HDL cholersterol concentrations. Intensive forms of physical activity provide addtional benefits as compared to light to moderated activities. Increasing duration of exercise provides addtional protection.

2.2.9 Cardiac diseases

Coronary heart disease, left ventricular hypertrophy, congestive heart failure, atrial fibrillation, and dilated cardiomyopathy are all associated with an increased risk of stroke (Wolf PA et al 1991). Cardioembolic events are known to be responsible for 20-30% of all ischemic strokes. Atrial fibrillation alone is associated with a 3- to 4-fold increased risk of stroke. The prevalence of atrial fibrillation increases with age. Atrial fibrillation affects about 5% of individuals over 70 years of age and the mean age of atrial fibrillation patients is 75 years. Strokes associated with atrial fibrillation are especially large and disabling. Antithrombotic drugs remain the mainstay for stroke therapy. With or without atrial fibrillation, all the patients with mechanical heart valves require anticoagulation therapy. The incidence of stroke is doubled in asymptomatic neck bruit. Almost 10% of stroke patients have had a transient ischemic attack and 40% of individuals who suffer a transient ischemic attack

will have a stroke within five years. The risk of stroke recurrence after the first stroke is about 13% in the first year and about 5% each year there after.

2.2.10 Other risk factors

Other risk factors of stroke are low socio-economic status, climate, season, family history of stroke, higher plasma levels of fibrinogen, transient ischaemic attacks, sickle cell disease, antiphospholipid antibodies, migraine, hyperhomocysteinemia, use of estrogen, dietary potassium and snoring.

2.3 Prevention of Stroke

The primary prevention of stroke is of vital importance to prevent loss of life and staggering costs. In primary prevention it is important to concentrate on the prevention of the development of atheroma, adequate treatment of hypertension and dyslipidemia and at the same time prevention of myocardial infarction, atrial fibrillation, diabetes mellitus and asymptomatic carotid artery disease. Lifestyle modifications such as a regular physical activity, consumption of a diet rich in fruits, vegetables and low-fat diary products and limited alcohol consumption are vital to prevent primary stroke. There is compelling evidence that good control of blood pressure (≤140/90) reduces the incidence of stroke regardless of age by 45%. Aspirin therapy is recommended in subjects with a high risk for coronary heart disease. However, there is not enough evidence to suggest that aspirin therapy reduces the risk of stroke in general population at low risk and that aspirin therapy would substantially prevent a first stroke after myocardial infarction. Antithrombotic therapy (warfarin or aspirin) is recommended in patients with atrial fibrillation. Randomized clinical trials have firmly established that adjusted-dose warfarin reduces the risk of stroke by 60% and aspirin by 20%. Subjects with type 2 diabetes have both an increased susceptibility to atherosclerosis and an increased prevalence of atherogenic risk factors, notably hypertension, obesity and abnormal blood lipids. It is not known if aggressive glycemic control reduces the risk of stroke. Adequate control of diabetes mellitus is recommended to reduce the risk of microvascular complications. Carotid endarterectomy is recommended in patients with asymptomatic carotid artery disease in case the carotid stenosis is in the order of ≥60% and ≤100%. However, it should be noted that most of the studies

were carried out before the widespread use of statins. Physically active lifestyles reducing dietary intake of saturated fats and alcohol, as well as cessation of smoking are all important in the prevention of stroke.

2.4 Exercise testing and Stroke

2.4.1 Exercise testing protocols

Present day exercise testing is not limited to the observation of ischemic ECG changes alone. Valuable and important information can be obtained from exercise capacity, heart rate and blood pressure responses, development of arrhythmias, and symptoms such as chest pain during exercise (Tavel ME, 2001). Factors that may improve the value of exercise testing include hemodynamic and chronotropic responses. This allows the assessment of the presence and severity of ischemia, prognosis, overall functional capacity, and the efficacy of therapeutic interventions. Electrocardiography, blood pressure, heart rate and exercise capacity remain the main measures used in everyday clinical practise and are the cornerstones for therapy (Tavel ME, 2001).

2.4.2 Bicycle exercise test

Exercise test on a cycle ergometer is non-weight bearing and can be used in those who are accustomed with cycling although they may have difficulties in walking and running. Electrically braked bicycles vary the resistance to the pedaling speed permitting good control of power output. The highest values of maximal oxygen uptake (VO_{2max}) and heart rate are obtained with pedaling speeds of 50 to 80 rpm, and therefore are the recommendable speeds (Fletcher GF et al, 2001). The main 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 pedalling speed. Leg fatigue in an non-experienced individual may cause him or her to stop before reaching a true VO_{2max}. VO_{2max} is generally around 10% to 15% lower in a cycle test than in a treadmill test in those who are not accustomed to cycling (Fletcher GF et al 2001, Hambrecht RP et al, 1992, Page E, et al 1994). Cycle ergometer produces less motion of the upper body and is less noisy than the treadmills.

Protocols for clinical exercise testing include an initial warm-up with a mild workload. It is a progressive uninterrupted exercise with increasing workloads with an adequate time interval at each level of exercise. During the various stages of cycle exercise including recovery period, various exercise test parameters are measured. The initial power output is commonly 10 to 20 Watts followed by increases of 20 to 25 Watts every 1 to 3 minutes until end point or maximal exercise capacity is reached. In Europe, 20 W increments per 1 minute are typically used during tests with cycle ergometer (Fletcher GF et al, 2001).

2.4.3 Blood pressure measurements during exercise

The measurement of blood pressure at each incremental workload and during recovery is an essential part of exercise testing. This measurement of blood pressure during exercise test has been shown to be a reasonably accurate method, although the reliability of sphygmomanometer in recording arterial pressure during maximal exercise has been questioned (Ramussen PH et al, 1985). It may not be easy to detect to Korotkoff sounds during exercise, especially when the subject is walking or jogging (Irving JB et al, 1977), and for this reason it is easier to measure SBP than diastolic blood pressure (DBP) during exercise. At times it may be difficult to obtain an accurate definition of

SBP due to body movements at high level of exercise and maximal effort (White WB et al, 1990).

Systolic blood pressure recorded intra-arterially and by sphygmomanometer are similar during exercise (Irving JB et al, 1977). Blood pressure is dependent on both cardiac output and peripheral resistance during exercise. Cardiac output at rest (5 to 6 L/min) increases to as high as 20 to 25 L/min during peak exercise, an increase proportional to the increase in exercise workload. As exercise progresses, SBP increases typically around 60 to 70 mmHg, whereas DBP changes very slightly as a result of vasodilatation and decrease in total peripheral resistance (Lim PO et al 1996). Systolic blood pressure at rest is a main determinant of maximal SBP during exercise. Maximal SBP during exercise has been found to be higher among those with hypertension. Gender, age, body weight cardiorespiratory fitness including cardioactive medication cardiorespiratory fitness and cardioactive medications have been known to affect blood pressure during exercise (Palatini P, 1998). The total rise in SBP was lowest among older and hypertensive subjects with CHD, whereas older men with CHD have smaller increases in blood pressure during exercise test. Physcially fit subjects may have higher maximal SBP and high total SBP rise due to their good exercise capacity (Fagard RH et al, 1996). The rise in blood pressure in trained subjects is a normal response of adaption due to increased cardiac output, where as in the untrained subjects increase in total peripheral resistance is the most likely mechanisms for the SBP variations. A minor rise or a fall in SBP during exercise is an abnormal response. A small rise can be due to severe left ventricular dysfunction, myocardial ischemia, aortic outflow obstruction and drug therapy (i.e. Beta-blockers).

2.4.4 Myocardial ischaemia during exercise

The long-standing use of exercise testing in the diagnostic and prognostic evaluation of patients with suspected or known CHD has shown the utility of functional capacity in various populations. ECG has been used to detect myocardial ischemia associated with obstructive and atherosclerotic CHD. The main application has been in the evaluation of patients with symptoms of angina or a previous clinical manifestation of CHD. Using ECG findings have been found to be angiographically demonstrable CHD, which is defined as greater than 50 % stenosis of major coronary arteries (Fowler-Brown A et al, 2004).

The predictive value of exercise ECG is dependent on the prevalence of CHD in the population tested. When it is used in a population with a low prevalence of CHD, such as an asymptomatic population including middle-aged subjects, these tests are expected to show low positive predictive values, whereas the majority of positive test results represent false-positive responses (Smith SC, Jr, et al, 2000). In a high risk population, a negative result cannot rule out CHD, though the results provide more prognostic information (Hill J and Timmis A, 2002) The yield of screening individuals with exercise testing has been greater in higher risk groups (Fowler-Brown A et al, 2004). Conclusions drawn from exercise tests are generally based on patients with chest pain, dyspnoe or discomfort, with certain patients being selected for further investigation in normal everyday practice.

The blood circulation supplies the brain and heart with nutrients and oxygen to maintain brain and cardiac function, and thus supply the rest of the body with blood. The ECG is monitored not only through out the exercise test but also after the exercise test. Changes in ST segment that are not apparent during the test may occur during the recovery period (Hill J and Timmis A,

2002). Multivessel or left main coronary disease has been found in approximately 90% of the patients who have changes appearing at very low workloads and persisting for up to 6-8 minutes after the exercise (Tavel ME, 2001). The occurrence of silent myocardial ischemia in asymptomatic middle-aged men is estimated to be around 2.5% under 60 years to 10% in men over 70 years (Fleg JL, et al 1990). Silent myocardial ischemia has been reported in almost all patients with symptomatic CHD (Cohn PF et al, 2003). Common changes caused by hyperventilation and postural changes such as T waves and ST-segment depression are mediated through the autonomic nervous system. Other changes may be due to digitalis administration, hypokalemia, postprandial changes, vasoregulatory and conduction defect changes. There is no common mechanism for ST changes in these diverse situations, however, the effects brought about by electrolyte changes and sympathetic nervous stimulation at the cellular level may play an important role (Fletcher GF et al 2001, Gibbons RJ et al 1997, Tavel ME, 2001).

2.5 Assessment of cardiorespiratory fitness

2.5.1 Indirect assessment of cardiorespiratory fitness

Cardiorespiratory fitness can be measured both indirectly and directly. The protocol should be tailored according to the indidvidual needs in order to yield a maximal fatigue-limited exercise duration of about 10-12 minutes (Myers J et al 1991, Lipinski M ety al 2002). Although the optimal duration for a protocol is 6 to 12 minutes of continuous and progressive exercise during which the oxygen demand on the myocardium is elevated to the individual´s maximal level that is optimal for both diagnosis and prognostic purpose. VO_{2max} can also be measured indirectly from the treadmill or cycle workload achieved. The indirectly measured exercise capacity should be normally

reported in estimated peak METs. The MET is defined as the ratio of the metabolic rate during exercise to the metabolic rate at rest. One Met is defined as oxygen uptake which is equivalent to 3.5 mL of oxygen consumption per kilogram of body weight per minute at rest. Exercise capacity can also be reported on the basis of duration of the exercise test.

2.5.2 Direct assessment of cardiorespiratory fitness

Directly measured VO_{2max} is a gold standard for assessing the amount of the oxygen consumption during a maximal effort (Fletcher GF et al 2001, Gibbons RJ et al 1997). It is considered the best measure of cardiovascular fitness and exercise capacity. Functional capacity is the ability of an individual to perform aerobic work as defined by the VO_{2max}. Directly measured VO_{2max} is the most reliablemeasure of cardiorespiratory fitness that can also provide an accurate assessment of functional capacity (Fletcher GF et al 2001,Sullivan M et al 1984). VO_{2max} is determined by the plateau of oxygen consumption 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 (Myers J et al 1991). 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 (Gibbons RJ et al 1997).

2.5.3 Determinants of cardiorespiratory fitness

VO_{2max} is the amount of oxygen a subject can take in from inspired air while performing dynamic exercise involving a large part of the muscle mass. It is considered the best measure of cardiovascular fitness and exercise capacity. Functional capacity is the ability of an individual to perform aerobic exercise

is defined as the VO_{2max}. VO_{2max} during exercise represents cardiac, circulatory and respiratory function and muscle oxygen utilization under physiological stress conditions. VO_{2max}, a product of cardiac output and maximal arteriovenous oxygen difference is determined by age, gender, the duration, intensity, frequency and type of physical activity, conditioning status, genetic factors and clinical or subclinical disease (Fletcher GF et al 2001). Age, gender and underlying diseases are determinants of initial cardiorespiratory fitness level, although they are not major determinants of human responses to regular physical activity. However, the pre-training level of a phenotype may contribute to the variability in training response in some individuals (Bouchard C and Rankinen T 2001, Bouchard C et al 2000, Rankinen T et al 2001). 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.

Although physical activity may be an appropriate therapy for the unfit subjects, inactivity may not be the only cause of being unfit when subclinical disease or genetic may be involved (Bouchard C and Rankinen T 2001, Williams PT 2001). Maximal values of VO_{2max} are observed during young age and decrease progressively with growing age. Since VO_{2max} is a measure of cardiorespiratory fitness, it is important to understand the relative contributions of genetic endowment and environmental influences in its determination. There are no previous cohort studies on directly measured cardiorespiratory fitness during exercise testing and the risk of stroke.

2.6 The role of exercise testing in risk prediction

Easily available noninvasive testing modalities have the potential to measure and to monitor atherosclerosis in asymptomatic high-risk subjects (Balady GJ et al 2000). Exercise ECG has been used as an important noninvasive testing method in a clinical practise. The presence of atherosclerosis risk factors identifies stroke patients at higer risk for cardiac events, as does the presence of carotid disease, a history of coronary disease, or myocardial ischemia. Myocardial ischemia is considered to be the most important cause of chest pain and is a consequence of underlying CHD. However, sometimes underlying 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 (Rodgers GP et al 2000). 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 (Mieres JH et al, 2005). Important other factors that may improve the value of exercise test include hemodynamic and chronotropic responses. Valuable information may be derived from blood pressure responses, exercise capacity, and heart rate, development of arrhythmias, and whether or not symptoms such as chest pain develop during the test (Tavel ME, 2001).

2.6.1 Exercise blood pressure and the risk of stroke

Systolic blood pressure changes at different workloads during an exercise test correspond to blood pressure changes in daily physical stress conditions (Palatini P, 1998, Fagard R et al 1991). Exercise-induced elevation in SBP has been found to increase the risk of future hypertension (Allison TG, et al 1999, Singh JP et al 1999, Ren JF et al 1985), left ventricular hypertrophy (Gottdiener JS et al 1990, Devereux RB and Pickering TG 1990), stroke (Kurl S et al 2001) and CVD death (Filipovsky J et al 1992, Mundal R et al 1996). An abnormal rise in exercise SBP in a subject with a normal resting pressure predicts increased risk for future hypertension (Allison TG, et al 1999). Elevated resting SBP is a common risk factor for stroke (Kannel WB, et al 1981). Incidence of stroke increases proportionally to blood pressure. SBP during exercise has been found to predict hypertension, (Singh JP et al1999, Allison TG et al, 1999, Manolio TA et al 1994,Goble MM and Schieken RM, 1991), CHD (Mundal R,et al 1996, McHam SAet al 1999) and CVD death (Lauer MS et al 1995, Filipovsky J et al 1992, Mundal R et al 1994). However, little is known about the association between SBP response to physical stress and the risk of stroke.

An excessive elevation of SBP during exercise testing has been a stronger predictor of mortality due to CVD than SBP at rest in some previous studies (Mundal R et al 1996, Mundal R et al 1994, Kjeldsen SE et al 1997). However, exercise SBP measurements have had only limited value in the evaluation of cardiovascular risk in hypertensive men compared with measurement of resting SBP (Fagard R et al 1991). Physical exercise capacity may have an effect on the SBP rise, because maximum exercise capacity varies among individuals. The problem with using SBP at a fixed workload as a measure of

blood pressure response is that individuals will perform at different percentages of their maximum capacity.

In a previous study, the highest CVD mortality rate was observed in men with both elevated resting and exercise blood pressure (Filipovsky J et al 1992) Fagard and co-workers (Fagard R et al 1991) reported that SBP at moderate and peak workloads was directly associated with the risk of cardiovascular events in hypertensive men. All these studies were based on cardiovascular events, but there have been no studies concerning SBP during progressive exercise testing and the risk of stroke. On the other hand, SBP may decrease more after exercise in fit and healthy persons than in unfit persons with a high risk of CVD.

2.6.2 Blood pressure during recovery from exercise

The rate of the SBP 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 (Erikssen J et al 1980). This finding is believed to be due to the recovery from the anaerobic metabolism that has occurred at peak exercise.

Because the recovery SBP is dependent on the magnitude of exercise and SBP at high workloads is difficult to record accurately, many investigators have been sceptical of the clinical usefulness of the ratio of exercise and recovery SBP. However, it appears that if accurate measures of SBP 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 due to inadequate reaction of vagal tone because of an increase in activity of the sympathetic nervous system (Jouven X et al 2005). Although blood pressure during recovery may also reflect cardiovascular reactivity after exercise, the

prognostic value of SBP after exercise has not been previously documented with respect to acute myocardial infarction.

2.6.3 Cardiorespiratory fitness and cardiovascular risk

Physical inactivity and low cardiorespiratory fitness are considered to be crucial health problems (McGinnis JM et al 1993). Previous studies have shown that physical activity (Blair SN et al 1984, Lakka TA et al 1994, Leon AS et al 1987, Morris JN et al 1980, Nelson L 1986, Paffenbarger RS Jr et al 1984) and good cardiorespiratory (Blair SN et al 1996, Sandvik L et al 1993, Ekelund L-G, et al 1988, Lakka TA et al 2001) fitness have protective effects on atherosclerotic cardiovascular disease, including CHD and hypertension. In addition, physical activity may protect against future stroke (Wannamethee G and Shaper AG 1992, Kannel WB and Sorlie P 1979, Salonen JT et al 1982, Paffenbarger RS Jr 1972, Paffenbarger RS Jr and Williams JL 1967, Sacco RL et al 1998), although the relation between physical activity and the risk for stroke has been inconsistent. One study, (Herman B et al 1983) reported a graded dose-response relation, whereas other studies (Menotti A and Seccareccia F 1985, Lee IM and Paffenbarger RS Jr 1998, Evenson KR et al 1999) have reported a nonlinear association between physical activity and the risk for stroke.

It is difficult to measure the total amount, duration, frequency, or intensity of habitual physical activity according to self-reported questionnaires. Some studies on physical activity and stroke risk have been based on crude physical activity measurements classified as low or high category during leisure time or at work (Salonen JT et al 1982, Paffenbarger RS Jr 1972). On the other hand, cardiorespiratory fitness measured directly by VO_{2max} during exercise testing

provides a quantitative measure of physical activity, although it is generally assumed that cardiorespiratory fitness represents mainly physical activity, besides other contributing factors such as age and heredity. One of the most important advantages of directly measured VO_{2max} is that it is an objective and quantitative measure of cardiorespiratory fitness.

Studies have found an association between physical activity at work (Salonen JT et al 1982) or during leisure time (Kannel WB and Sorlie P 1979, Paffenbarger RS Jr 1972, Paffenbarger RS Jr and Williams JL 1967, Herman B et al 1983) and subsequent risk for stroke. Leisure-time physical activity has been related to a decreased risk for ischemic stroke (Sacco RL et al 1998). Furthermore, low levels of occupational physical activity have been shown to increase the risk for stroke (Paffenbarger RS Jr 1972). However, some studies have provided an indication of a U-shaped relationship between physical activity and stroke (Menotti A and Seccareccia F 1985, Lee IM and Paffenbarger RS Jr 1998, Evenson KR et al 1999). High-intensity exercise is more effective than low-intensity exercise for improving VO_{2max} in healthy persons, whereas lower-intensity physical activity may be sufficient to improve VO_{2max} in high-risk individuals. However, there are no cohort studies concerning the association between cardiorespiratory fitness and the risk for stroke.

2.6.4 Silent myocardial ischaemia and cardiovascular risk

Previous studies have shown that exercise-induced myocardial ischemia increases the risk of future coronary events in both patients with CHD Falcone C et al, 1987, Detrano R et al 1989, Mark DB et al 1989, Miranda CP, et al 1991, Weiner DA et al 1978, Bonow RO et al 1987), and asymptomatic individuals with no prior CHD (Bruce RA et al 1983). The likelihood of

detecting myocardial ischemia is known to be higher among those with an increased pretest probability of CHD, such as asymptomatic, high-risk individuals (Fleg JL et al 1990, Ekelund L-G, et al 1988). Little is known about the prognostic value of exercise-induced silent myocardial ischemia in high- and low-risk individuals, however with respect to stroke.

Some evidence shows that ECG findings may predict the risk of stroke (Knutsen R et al 1988, Chua HC et al 1999). Ischemic ST-segment changes during exercise are considered a marker of myocardial ischemia due to underlying coronary atherosclerosis. It is also possible that myocardial ischemic ST-segment changes may indicate an increased risk of other CVDs because of generalized atherosclerosis. Furthermore, ischemic ST-segment changes in the presence of common risk factors such as hypertension, smoking, hypercholesterolemia, and overweight may increase the probability of CHD. However, there are no evidence exploring whether silent, exercise-induced, ST-segment depression predicts the risk of CVDs and cerebrovascular diseases in high-risk individuals.

It is plausible that silent myocardial ischemia on ECG testing is a reflection of advanced atherosclerosis, not only in the coronary arteries but also in large arteries of the cerebral circulation (Knutsen R et al 1988, Chua HC et al 1999). Because atherosclerosis is the pathological basis of occlusive cerebrovascular disease, it may partly explain the association between exercise-induced myocardial ischemia and stroke. CHD and stroke share several risk factors, and an association between atherosclerotic cerebrovascular disease and CHD has been established in several studies (Miranda CP, et al 1991, Chua HC et al 1999, Lakka TA et al 1994).

2.6.5 Exercise cardiac power and the risk of stroke

Previous studies showed that low VO_{2max} and elevated SBP during exercise have been associated with the risk of stroke (Kurl S et al2003). Because exercise cardiac power (ECP) is a function of cardiac output (VO_{2max}) and peripheral resistance (SBP), it may improve the predictive value of VO_{2max} alone. VO_{2max} is considered a golden standard for measuring cardiorespiratory fitness. In addition to VO_{2max}, SBP can be measured more reliably during cycle ergometry. It has been suggested that VO_{2max} is a noninvasive measure of cardiac output during physical stress and reflects cardiac preload, whereas SBP is a mere indicator of afterload during exercise. Cardiac output is dependent on preload and afterload. In subjects with elevated adrenergic tone and inappropriately constricted arterial bed, cardiac output can be lowered in the presence of disproportionately elevated SBP (Zelis R and Flain SF 1982). Consequently, VO_{2max} may be severely reduced, and thus, it may underestimate cardiac pumping capacity in a large number of subjects. ECP takes into consideration not only the preload but also afterload that potentially increases its value as a prognostic marker for stroke. The impairment of coronary or cerebral blood flow and cardiac function during exercise may be caused by dynamic coronary or carotid artery stenosis as a result of vessel constriction, endothelial dysfunction, spasm, and thrombosis (Zelis R and Flain SF 1982, Bain RJ et al 1990, Saxon LA et al 1993). A high intraluminal pressure will lead to extensive change in endothelium and smooth muscle function in intracerebral arteries. Endothelial damage and change in blood cell–endothelium interaction can lead to local thrombi formation and ischemic lesions. Because ECP is a function of cardiac output (VO_{2max}) and peripheral resistance (SBP), it may improve the predictive value

of VO$_{2max}$ alone.

2.7 Summary of the review of literature

Exercise test has been a valuable clinical tool for assessing therapy in patients with various cardiovascular diseases. Exercise is the body´s most common physiologic stress, which places major demands on the cardiovascular system. Changes in hemodynamism and metabolism lead to changes in blood pressure also during exercise. However, the prognostic value of SBP during and immediately after maximal exercise testing is not well known with respect to stroke. Cardiorespiratory fitness and ischemic ECG changes can be defined during exercise test. Painful and painless ischemic changes during exercise test are risk predictors for ischemic cardiac events although little is known about the role of silent myocardial ischemia among men with coexisting risk factors and the risk of stroke.

Although VO$_{2max}$ can be held as a predictive marker of cardiovascular capacity, it does not take into account the differences in cardiovascular resistance and cardiac afterload between the subjects. In addition to resting SBP, exercise-induced elevation of SBP has been found to be an independent predictor of stroke. SBP at peak exercise and VO$_{2max}$ are the two variables that are useful in risk stratifying for stroke. ECP takes into consideration not only the preload but also afterload that potentially may increase its value as a prognostic marker for stroke. Evidence also suggests that even more attention should be layed on the recovery period using ECG and SBP recordings after the cessation of maximal exercise.

3 AIMS OF THE STUDY

a) to study the associations between SBP rise, percent maximum SBP at two minutes post-exercise and the risk of stroke in men with no prior CHD.

b) to assess whether exercise-induced silent ST-segment changes are related to the risk of future strokes and cardiovascular diseases in men with and without conventional risk factors.

c) to examine the relationship of cardiorespiratory fitness, as indicated by maximal oxygen uptake, with subsequent incidence of stroke and compare maximal oxygen uptake with conventional risk factors as a predictor for future strokes.

d) to study the relationship of cardiac power during exercise defined as the ratio of maximal oxygen uptake with peak systolic blood pressure to the risk of stroke.

4 METHODS

4.1 Study population

The study was carried out on 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 including stroke (Salonen JT 1988). The study involves men from eastern Finland (Table 1), an area known for its high prevalence and incidence of atherosclerotic vascular diseases (Keys A et al 1984). The study population 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.

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).

Table 1. The description of the study population and main variables.

Study	n	Population	Test variable	Follow-up Time	Main Outcomes
I	1026	With no stroke, CHD and antihypertensive medication	Systolic blood pressure during exercise and maximal oxygen uptake	10.4 years	46 strokes, 38 ischaemic strokes
II	1769	With no stroke, CHD and atrial fibrillation	Exercise ECG chages indicating painless myocardial ischemia	10.0 years	78 strokes, 86 CVD deaths
III	2011	With no stroke and pulmonary disease	maximal oxygen uptake and exercise duration	11.0 years	110 strokes, 87 ischaemic strokes
IV	1761	With no stroke and CHD	Cardiac power during exercise	12.0 years	91 strokes, 69 ischaemic strokes

4.3 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 SBP was the highest value achieved during the test. Blood pressure was measured during recovery at two minutes intervals regularly while subjects were seated on the cycle without pedalling (Kurl S et al 2001). Post-exercise measurements, were made regularly every two minutes. Blood pressure measurements at two minutes were selected as the main variable because data was available for all men. The SBP difference between rest and recovery was calculated as SBP at recovery from exercise minus SBP at rest.

4.4 Assessment of exercise electrocardiography

ECG was recorded continuously with the Kone 620 electrocardiograph (Kone, Turku, Finland). The Mason-Likar lead system including Vl, V5 and aVF lead connections was used (Mason RE and Likar I 1966). 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 cardiorespiratory fitness

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

4.6 Assessment of exercise cardiac power

VO_{2max} and SBP were assessed with a maximal symptom-limited exercise-tolerance test on an electrically braked bicycle ergometer. All the men underwent a testing protocol with a step-by-step increase in the workload by 20 W per minute.

4.7 Biochemical analyses

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 (Salonen JT et al 1991). 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). Plasma fibrinogen was determined based on clotting of diluted plasma with excess thrombin using a Goagulometer KC4 device (Heinrich Amelung, Lemgo, Germany).

4.8 Resting blood pressure

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 (Hawksley, Lancing, U.K.).

4.9 Obesity

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

4.10 Smoking and alcohol consumption

Smoking was assessed by 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.

4.11 Physical inactivity

Physical activity was assessed using the KIHD 12-Month Leisure-Time Physical Activity Questionnaire (Lakka TA et al 1994). 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 at the time of the interview.

4.12 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 nitroclycerin 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 6.7mmol/L or a clinical diagnosis of diabetes with either dietary, oral or insulin treatment.

4.13 Collection and classification of follow-up events

Incident strokes between 1984 and 1992 were ascertained through the Finnish part of Monitoring of Trends and Determinants in Cardiovascular Diseases (FINMONICA) stroke register (Kurl S et al 2003, Kurl S et al 2001). Information on stroke incidence between 1993 and December 31, 1999, was obtained by computerized linkage to the Finnish national hospital discharge registry and death certificate registers. Diagnostic information was collected from hospitals and classified by a neurologist with diagnostic criteria identical to the FINMONICA criteria. The sources of information on stroke were hospital documents, death certificates, autopsy reports, and medico–legal reports. The diagnosis of stroke was based on sudden onset of clinical signs or focal or global disturbance of cerebral function lasting >24 hours (except in the case of sudden death or if interrupted by surgical intervention) with no apparent cause other than a vascular origin. Each suspected stroke

(*International Classification of Diseases, 9th Revision* [ICD-9] codes 430 to 439 and ICD-10 codes I60–I68 and G45–G46) was classified into: (1) a definite stroke, (2) no stroke, or (3) unclassifiable events. The FINMONICA stroke register data were annually rechecked with the data obtained from the computerized national hospital discharge and death registers. Definite strokes and unclassifiable events were included in the group of any stroke. Each definite stroke was classified into: (1) an ischaemic stroke (ICD-9 codes 433 to 434, ICD-10 code I63) or (2) a haemorrhagic stroke (ICD-9 codes 430 to 431, ICD-10 codes I60–I61). If the subject had multiple nonfatal strokes during follow-up, the first stroke was considered as the end point. Computed tomography (CT) was performed in 90% of the cases by 1993, and CT, MRI, and autopsy reached 100% by 1997.

4.14 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. 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 P value less than 0.05 was considered statistically significant.

4.14.1 Study I

The associations of SBP during exercise and recovery with the risk of stroke were analyzed with SPSS Cox proportional hazards' models. Covariates were entered as uncategorized into Cox models. Covariates were selected by entering common stroke risk factors (age, smoking, serum LDL cholesterol, diabetes, BMI, and alcohol consumption) in forced Cox models. When the predictive values of resting and exercise SBP were compared, additional multivariate analyses were performed. In these analyses, resting and exercise SBP were entered simultaneously in a forced Cox model with other presented covariates. Relative hazards adjusted for risk factors were estimated as antilogarithms of coefficients from multivariate models.

4.14.2 Study II

Differences in baseline characteristics between men with and without silent myocardial ischemia during exercise were analyzed by Student's t test. The associations of silent myocardial ischemia during exercise with the risk of stroke and CVD death were analyzed by risk factor–adjusted, forced Cox proportional-hazards models. Wherever possible, confounding factors were entered uncategorized into the Cox models. Relative hazards, adjusted for age, examination years and the well-known risk factors (smoking, alcohol consumption, SBP, BMI, diabetes, and serum LDL cholesterol) for CVDs and stroke were estimated as antilogarithms of coefficients for independent variables.

The modification of risk factors was analyzed by comparing the prognostic value of silent myocardial ischemia among (1) smokers and nonsmokers, (2) men with higher ($\geqslant$3.5 mmol/L) and lower (<3.5 mmol/L) serum LDL cholesterol levels, (3) hypertensive and normotensive men, and (4) overweight

to obese ($\geq$25 kg/m²) and normal-weight (<25 kg/m²) men.

4.14.3 Study III

We examined the associations of VO₂max with the risk factors for strokes by covariate analyses and with the risk for stroke by Cox proportional hazards modelling. The levels of VO₂max were entered as dummy variables into forced Cox models. In these analyses, VO₂max was divided according to quartiles. Covariates were entered uncategorized, when possible, into the Cox models. The following two different sets of covariates were used: (1) age and examination years, and (2) age, examination years, cigarette smoking, alcohol consumption, socioeconomic status (SES), energy expenditure of physical activity, prevalent CHD, diabetes, SBP, and serum LDL cholesterol level. We analyzed the predictive power of fully adjusted Cox models by representing receiver operating characteristic curves of these models together with the risk factors. The association between other conventional risk factors and the risk for stroke was analyzed in the Cox model entering SBP, BMI, alcohol consumption, and serum LDL cholesterol level as quartiles except for smoking (yes or no), with age and examination years adjusted into models. The fit of the proportional hazards models was examined by plotting the hazard functions in different categories of risk factors over time.

4.14.4 Study IV

The associations of ECP with the risk factors for strokes were examined using covariate analyses and with the risk of stroke by Cox proportional hazards modeling. The levels of ECP were entered as dummy variables into forced Cox models. In these analyses, ECP was divided according to quartiles. Covariates were entered uncategorized, when possible, into the Cox models.

Two different sets of covariates were used: (1) age and examination years, and (2) the use of antihypertensive medication, cigarette smoking, alcohol consumption, BMI, the energy expenditure of physical activity, diabetes, exercise-induced myocardial ischemia, and serum LDL cholesterol. To show the independent relationship between ECP and risk of stroke, resting SBP was included in model 2.

5 RESULTS

5.1 Systolic blood pressure during exercise and the risk of stroke

5.1.1 Systolic blood pressure at baseline

Mean resting SBP in the entire study population was 129 mm Hg (range 91 to 207 mm Hg. Resting SBP correlated positively with SBP immediately before the exercise test while subjects were seated on the bicycle (r=0.70, p<0.001), SBP at two (r=0.64, p<0.001) and four minutes of exercise (r=0.61, p<0.001), SBP rise per minute of exercise duration (r=0.30, p<0.001), maximum SBP (r=0.42, p<0.001), and SBP at two minutes after exercise (r=0.53, p<0.001). The rise in SBP appeared to plateau after 10 minutes of exercise.

Figure 1 below shows mean and standard deviation of systolic blood pressure measured during maximal symptom-limited exercise stress test every 2 minutes in men free of stroke, coronary heart disease and antihypertensive medications at baseline.

Exercise duration/ minutes
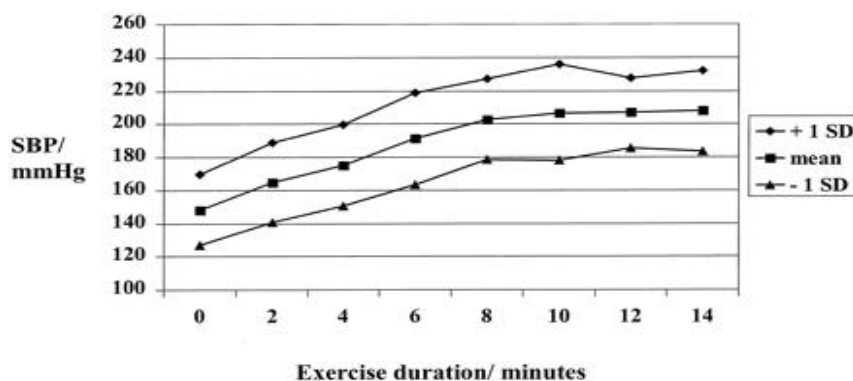
5.1.2 Systolic blood pressure at moderate workloads

One SD increment of SBP at two and four minutes from the start of the exercise test was associated with an increased risk of stroke. If resting SBP was added into the forced models, the relationship of SBP at two and four minutes and resting SBP was not significant. Maximum SBP was not associated with the risk of stroke.

5.1.3 Systolic blood pressure rise during exercise test

The SBP rise per minute of exercise duration was associated with the risk of stroke. One SD increment of SBP rise per minute (18.8 mm Hg) was associated with a 2.3-fold increased risk of any stroke and a 2.3-fold increased risk of ischaemic stroke. After further adjustment for resting SBP, SBP rise per minute of exercise duration was associated almost statistically significantly with the risk of any stroke (RR=2.06, 95% CI 0.99 to 4.49, p=0.051). Men with an SBP rise >19.7 mm Hg per minute of exercise duration had a 2.3-fold increased risk of any stroke and a 2.3-fold increased risk of ischaemic stroke compared with men whose SBP rise was <16.1 mm Hg/min. Additionally,

exercise duration was related to the risk of stroke after adjustment for other known risk factors, excluding maximum oxygen uptake. Maximum oxygen uptake correlated strongly with exercise duration (r=0.71, p<0.001).

5.1.4 Percent maximum systolic blood pressure at 2 minutes after exercise

High SBP after exercise was related to an increased risk of stroke. The RR was 1.6 for any stroke and 1.7 for ischaemic stroke at two minutes of recovery for an increment of 1 SD. After further adjustment for resting SBP, the respective RRs were 1.47 (95% CI 1.01 to 2.15, p=0.04) for any stroke and 1.58 (95% CI 1.03 to 2.43, p=0.03) for ischemic stroke. Percentage of SBP at two minutes after exercise of maximal SBP was related to an increased risk of stroke. A high ratio of SBP at two minutes of recovery and maximum exercise (highest tertile) was associated with a 4.6-fold increased risk of any stroke and a 5.1-fold increased risk of ischaemic stroke.

5.2 Exercise-induced silent myocardial ischemia, stroke and cardiovascular mortality

5.2.1 Silent myocardial ischemia at baseline

Serum LDL cholesterol, resting SBP, maximal heart rate, and rate-pressure product were higher in men with silent myocardial ischemia during exercise and the number of cigarettes smoked lower in men. There were no significant differences in other baseline characteristics between men with and without silent ischemia during exercise.

In this study sample, there were 123 (7.1%) men with silent ischemia during exercise. Silent ischemia during exercise was observed in 5.4% (n=28) of smokers, in 8.3% (n=89) of hypercholesterolemic men, in 7.7% (n=68) of

hypertensive men, and in 6.0% (n=69) of overweight men.

5.2.2 Stroke risk and cardiovascular mortality

Men with silent ischemia during exercise had a 2.2-fold increased risk of stroke and a 3.5-fold increased risk of CVD death compared with men without silent ischemia, after adjusting for conventional risk factors. Silent ischemia after exercise was associated with a 5.2-fold increased risk of CVD death but was not associated with the risk of stroke. The cumulative hazard curves for CVD death and stroke continued to diverge during the follow-up period Also, milder silent ischemia (defined as a horizontal or downsloping ST-segment depression of 0.5 to 0.9 mm) during exercise was related to an increased risk of CVD death (RR=3.0; 95% CI, 1.5 to 6.0, p=0.001).

Figure 2 below shows cumulative hazards of cardiovascular mortality in men with silent myocardial ischemia (high-risk group) during exercise versus all others (low-risk group

Years of follow-up
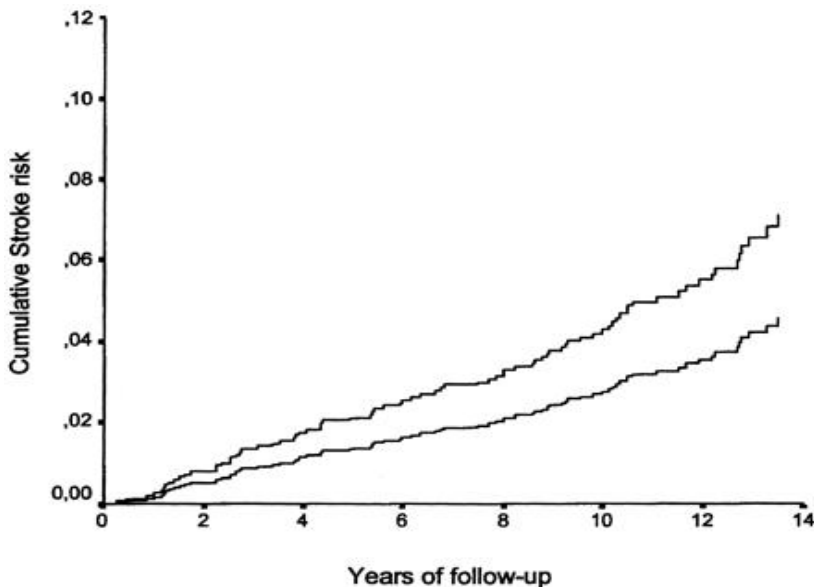
5.2.3 Interactions of silent ischemia and risk factors

Silent ischemia during exercise had a stronger association with the risk of CVD death and stroke in smokers and in hypercholesterolemic, hypertensive, and overweight men than in men without such risk factors. Silent ischemia during exercise had a strong association with the increased risk of CVD death in smokers (RR=3.8; 95% CI, 1.5 to 9.5), in hypercholesterolemic men (RR=3.9; 95% CI, 2.1 to 7.3), in hypertensive men (RR=3.6; 95% CI, 1.9 to 6.8), and in overweight men (RR=3.8; 95% CI, 2.0 to 7.1). The respective relative risks of stroke were 3.8; (95% CI, 1.1 to 12.5) in smokers; 3.5 (95% CI, 1.7 to 7.4) in hypercholesterolemic men; and 3.4 (95% CI, 1.6 to 7.1) in hypertensive men with any risk factor. All of these associations were statistically nonsignificant in men without any conventional risk factors, except for nonsmokers with silent ischemia during exercise, who also had an increased risk of CVD death (RR=3.2, 95% CI, 1.6 to 6.4). Silent ischemia during exercise had a strong association with the risk of stroke in men with both hypertension and hypercholesterolemia (RR=6.1, 95% CI; 2.4 to 15.4) and in smokers with hypercholesterolemia (RR=5.6; 95% CI, 1.8 to 18.2), as well as in smokers with hypertension (RR=10.2; 95% CI, 2.5 to 42.7). The respective RR for CVD death was 3.2 (95% CI, 1.7 to 6.0) in men with hypertension and hypercholesterolemia, 4.1-fold (95% CI, 1.9 to 9.0) in smokers with hypercholesterolemia, and 8.4-fold (95% CI, 4.3 to 16.4) in smokers with hypertension. In men with silent ischemia and three conventional risk factors (hypertension, hypercholesterolemia, and smoking), the RR of stroke was 4.9 (95% CI, 1.51 to 15.9). The risk of CVD death was 5.8 (95% CI, 2.3 to 14.7). However, decreased statistical power limits the interpretation of the results among the few asymptomatic subjects (n=18) with all 3 risk factors and silent ischemia during exercise. Silent myocardial ischemia in overweight men when

combined with hypertension (5.8-fold risk) and hypercholesterolemia (3.6-fold risk) was related to the increased risk of stroke, except for overweight smokers, who had no statistically significantly increased risk for stroke. Silent myocardial ischemia was related to a 3.9-fold (95% CI, 1.9 to 7.9) increased risk for CVD death in overweight smokers, a 3.9-fold (95% CI, 1.7 to 6.0) increased risk in overweight and hypertensive men, and a 4.1-fold (95% CI, 1.7 to 10.3) increased risk in overweight and hypercholesterolemic men.

5.3 Cardiorespiratory fitness and the risk of stroke
5.3.1 Cardiorespiratory fitness at baseline

As continuous variables, the strongest and statistically significant risk factors for any stroke were VO_{2max} (p<0.001), SBP (p<0.001), SES (p<0.001), and diabetes (p = 0.02) after adjustment for age and examination years. The respective risk factors of ischaemic stroke as continuous variables were VO_{2max} (*p*<0.001), SBP (p<0.001), SES (p<0.001), and diabetes (*p* =0 .003). One SD increase in VO_{2max} (3.5 mL/kg per minute) decreased the risk for any strokes by 17% (95% CI, 14%-8%) and ischemic stroke by 17% (95% CI, 25%-8%). For testing the discriminatory power of the adjusted Cox model, we included age, examination years, smoking, alcohol consumption, SES, energy expenditure of physical activity, prevalent CHD, diabetes, SBP, and serum LDL cholesterol level into the same model. The area under the curve was 0.72 (95% CI, 0.68-0.78) for ischaemic stroke. After adding the VO_{2max} into the model, the receiver operating characteristic curve value was 0.74 (95% CI, 0.67-0.76), representing good discriminatory power of the model adjusted for the risk factors.

5.3.2 Cardiorespiratory fitness, risk factors and stroke risk

Cardiorespiratory fitness was inversely related to the risk of stroke. Low cardiorespiratory fitness was associated also with an increased risk of any stroke and ischaemic stroke. Men with low cardiorespiratory fitness (VO_{2max}, <25.2 mL/kg per minute [lowest quartile]) had a 3.24-fold risk for any stroke (95% CI, 1.71-6.12; p<.001; p<0.001 for linear trend across the quartiles) and a 3.50-fold risk for ischaemic stroke (95% CI, 1.66-7.41; p = 0.001; p<0.001 for linear trend across the quartiles), compared with men who had high cardiorespiratory fitness (VO_{2max} >35.3 mL/kg per minute [highest quartile]) after adjusting for age and examination years. Low cardiorespiratory fitness was associated with a 2.30-fold risk for any stroke and a 2.40-fold risk for ischaemic stroke, after additional adjustment for conventional risk factors. When we excluded men with prevalent CHD (n = 677), low cardiorespiratory fitness (VO_{2max}, <25.2 mL/kg per minute) was related to a 1.93-fold risk for stroke (95% CI, 1.10-3.22; p = 0.02) after adjustment for conventional risk factors. Hypertensive men (SBP, >143 mm aHg) had a 2.73-fold risk for any stroke and a 2.97-fold risk for ischemic stroke compared with men with SBP of less than 122 mm Hg. Furthermore, men with slightly increased SBP (133-143 mm Hg) had a more than 2-fold risk for any stroke, as shown in. Obesity (BMI >28.8) was associated with a greater than 2-fold risk for any stroke and ischemic stroke. On the other hand, alcohol consumption had a protective effect because men who drank moderate amounts of alcohol had a reduced risk for stroke, indicating a U-shaped association between alcohol consumption and stroke. Men consuming alcohol 6.1 to 31.8 g/wk had a relative risk of 0.55 for any stroke and 0.54 for ischemic stroke. Serum LDL

cholesterol level and smoking were not significantly associated with the risk for strokes in our study population.

5.4 Exercise cardiac power during exercise and the risk of stroke

5.4.1 Exercise cardiac porwer at baseline

In the beginning of the follow-up, the mean age of the healthy subjects was 52.0 years (range 42.0 to 61. 3 years). The mean ECP was 12.45 mL per mm Hg (SD 3.08 mL/mm Hg; range 4.35 to 29.57 mL/mm Hg). At baseline examination, men with low ECP were older and they smoked more, had higher serum LDL cholesterol, SBP, and DBP, higher prevalence of diabetes, and were less active physically and consumed more alcohol compared with those who had higher ECP.

5.4.2 Exercise cardiac power and stroke risk

One SD increase in ECP (3.08 mL/mm Hg) was associated with a 32% (95% CI, 47% to 12%) decreased risk of any stroke and a 31% (95% CI, 48% to 8%) ischaemic stroke. One SD increase in VO_{2max} (539.7 mL/min) was not associated with a decreased risk of any stroke (RR, 0.8; 95% CI, 0.6 to 1.0; p=0.102) and ischemic stroke (RR, 0.82; 95% CI, 0.62 to 1.10; p=0.136) after adjustment for risk factors. Change in maximal SBP (SD 26.5 mm Hg) was not related to the risk of any stroke (RR, 1.11; 95% CI, 0.91 to 1.40; p=0.261) or ischaemic stroke (RR, 1.1; 95% CI, 0.90 to 1.40; p=0.402).

ECP was related inversely to the risk of stroke. Men with low ECP (<10.3 mL/mm Hg, lowest quartile) had a 2.9-fold (95% CI, 1.3 to 6.1; p=0.007) risk of any stroke compared with men who had high ECP (>14.3 mL/mm Hg, highest quartile) after adjusting for age and examination years (p=0.01 for linear trend

across quartiles). Low ECP was associated with a 2.7-fold risk of any stroke after additional adjustment for conventional risk factors (p=0.03 for linear trend across the quartiles. After further adjustment for SBP response, defined as total rise in SBP from start to peak exercise, the respective RR among men with low ECP was 2.5 (95% CI, 1.23 to 4.91; p=0.01). Similar results were observed after further adjustment for the change in SBP during exercise divided by resting SBP (RR, 2.32; 95% CI, 1.18 to 4.58; p=0.015). After additional adjustment for resting SBP, the respective RR among men with low ECP was 2.09 (95% CI, 0.96 to 4.57; p=0.06). In a subanalysis among fit men (VO$_{2max}$ of >32.4 mL/kg per minute), a significant risk was observed in men with low ECP compared with those with high ECP.

Low ECP was also associated with an increased risk of ischaemic stroke. Men with low ECP had a 2.9-fold (95% CI, 1.50 to 7.30; p=0.001) risk of ischaemic stroke relative to those with high ECP after adjusting for age and examination years and with a 2.7-fold risk of ischemic stroke after further adjustment for conventional risk factors. After additional adjustment for resting SBP, men with low ECP had a 2.27-fold (95% CI, 0.89 to 5.78; p=0.08) risk for ischaemic stroke.

5.4.3 Exercise cardiac power, systolic blood pressure at rest and stroke risk

There was a significant interaction between ECP and resting SBP and the risk of ischemic stroke (p=0.01 for interaction). Men with low ECP (<13.12 mL/mm Hg, median) and of elevated resting SBP (>132 mm Hg, median) had a markedly increased risk of any stroke and ischaemic stroke. Low ECP with elevated resting SBP was related to a 2.63-fold (95% CI, 1.30 to 5.32; p=0.007) increased risk compared with men with high ECP and low resting SBP. Men with low ECP and high SBP at rest had also a 2.53-fold (95% CI, 1.01 to 5.45;

p=0.04) increased risk of ischaemic stroke. The figure below shows age- and examination-year adjusted risk for stroke among hypertensive and normotensive men according to low exercise cardiac power (< 13.12 ml/mm HG) and high exercise cardiac power(≥ 13.12 mL/mm Hg).

*p=0.007
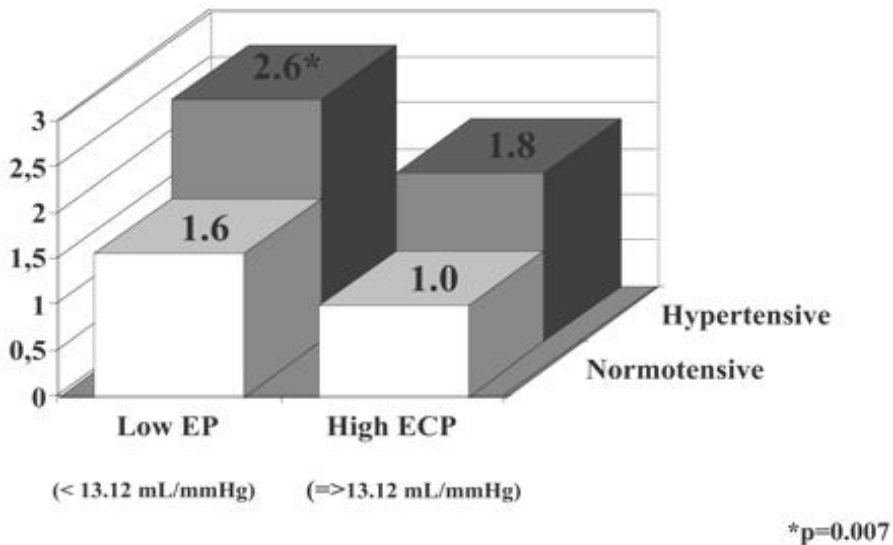
The figure 3 above shows age- and examination-year adjusted risk for stroke among hypertensive and normotensive men according to low exercise cardiac power (< 13.12 ml/mm HG) and high exercise cardiac power(≥ 13.12 mL/mm Hg).

6. DISCUSSION

6.1 Methodological aspects

6.1.1 Epidemiologic study

Prospective epidemiological studies lead the way in showing associations between the various risk factors of interest and cardiovascular outcomes. In

large population based samples of subjects, asymptomatic disease may change underlying risk factors so that the associations are either concealed or causation reversed. These factors may cause confounding and lack of independence (Brotman DJ et al 2005). There may be a threshold relationship rather than linear association between the risk factor and the outcome event. Difficulties in measurement and within person variability may underestimate the true effects. On the basis of our study, however, the inverse association between cardiorespiratory fitness and stroke was linear. An independent risk factor such as low physical fitness does not always mean a causal relationship, and risk factor such as physical inactivity that has a causal relationship will not necessarily prove to be an independent risk factor. Neither, high ranking of a risk factor does not guarantee causality, nor does low ranking indicate a weak relationship. Nevertheless, the strength and independence of the association is an additional evidence for causality. Moreover, it should be realized that an independent predictor has meaning only in the context of a particular model which includes well known and established risk factors (Brotman DJ et al 2005).

The present prospective population study provides strong evidence that cardiorespiratory fitness, cardiac power, exercise ECG findings and SBP during recovery from exercise are associated with the risk of stroke. These findings emphasize the prevention of stroke in high risk populations. The CVD epidemic arises from the interaction between a widespread individual susceptibility to disease due to heredity and environmental risk factors, such as unhealthy diet, lack of exercise, and smoking (Smith SC Jr et al 2000, Lenfant C 1994, Shephard RJ and Balady GJ 1999). Regular emphasis should be laid on the development of prevention skills in clinical practice both in both preventive cardiology and neurology (Shephard RJ and Balady GJ 1999).

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. Also the participation rate was high and there were no losses to follow-up. Our study provided a valuable opportunity to show the prognostic value of exercise testing with respect to stroke risk in a population based sample of men. The study protocol provided possibility to investigate the predictive value of exercise testing variables in men with different risk profiles. The study represents a sample of middle-aged male population from eastern Finland, an area known for its high incidence of atherosclerotic vascular diseases. 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 and other populations as well. However, on the basis of some previous studies (Gulati M et al 2003, Mora S et al 2003, Gulati M et al 2005), there is no evidence to suggest that the prognostic value of exercise capacity would be different among female subjects.

6.1.3 Exercise testing

Cycle ergometer and treadmill are two mainly used exercise testing methods. Cycle ergometer is the preferred modality in Europe whereas treadmill exercise is generally the preferred modality in the United States. Cycle ergometer test can be recommended for those who are overweight or have joint diseases limiting walking or running, because exercise on a bicycle is non-weight-bearing whereas walking on treadmill requires a good ability to

maintain walking speed and balance (Fletcher GF et al 2001, Fleg JL et al 2000). It is argued that some untrained subjects will terminate cycle exercise because of quadriceps muscle fatigue. Cycle ergometry may be preferred mode when hemodynamic monitoring such as blood pressure is required. Upper body motion is less, and hence it makes it easier to measure blood pressure and to record the ECG.

The use of direct measure of VO_{2max} has the benefit of providing a valuable assessment of cardiorespiratory fitness using different exercise protocols (Fletcher GF et al 2001, Revill SM et al 2002). As oxygen consumption is determined primarily by cardiac output in the absence of pulmonary or skeletal limitations, this allows the use of VO_{2max} as an estimate of cardiovascular function during physiological stress. However, from a practical point of view, large studies estimate the level of cardiorespiratory fitness by the measurements of the duration of exercise the workload achieved during the exercise test. Exercise capacity can be used as an additional noninvasive tool for outcomes providing clinically relevant diagnostic and prognostic information for CVDs including stroke. Since direct measurement of the volume of oxygen consumed requires specialized equipment, many studies estimate cardiorespiratory fitness by using indirect assessment of exercise capacity.

Exercise testing by a cycle ergometer usually consists of progressive incremental workloads which may have a little effect on SBPs achieved between the cycle and the treadmill exercise testing protocols. In our study, both the conventional indirect definition of exercise capacity, as well as, the respiratory gas analysis were used which is unique in a large population study.

6.2 Systolic blood pressure during exercise and the risk of stroke

SBP rise during exercise provides information about the hemodynamic response to increasing physical stress that is not available from SBP at rest. Dynamic exercise produces a large increase in SBP without much change in DBP (McHam SA et al 1999). In a previous study, the highest CVD mortality rate was observed in men with both elevated resting and exercise blood pressure Filipovsky J et al 1992. Fagard et al, reported that SBP at moderate and peak workloads was directly associated with the risk of cardiovascular events in hypertensive men (Fagard R et al 1991). All these studies were based on cardiovascular events, but there were no studies concerning SBP during progressive exercise testing and the risk of stroke. We determined that both SBP at moderate fixed workloads and the SBP rise per minute of exercise were associated with an increased risk of any stroke. Furthermore, hypertension accelerates the atherosclerotic process in carotid and vertebral arteries (Allison TG et al 1999, Lakka TA et al 1999), which usually starts in the larger extracerebral arteries, particularly in the carotid bifurcation. This process, with time, spreads distally to the smaller intracerebral arteries, leading to increased vascular resistance and hypertension during exercise and hence the increased risk of cardiovascular events (Hashimoto M et al 1993). This mechanism may be the same for the development of stroke in men with high SBP during exercise. It is possible that the steep rise in exercise blood pressure produces poor arterial compliance. This causes a higher SBP rise in subjects with underlying arteriosclerotic disease or structural vascular changes and vice versa (Palatini P 1998). With increasing age, blood vessels become less elastic, and peripheral vascular resistance also increases in older

normotensive individuals, which may be one reason for the steep rise in SBP at physical stress compared with elevation of SBP at rest.

6.3 Systolic blood pressure during recovery from exercise and the risk of stroke

SBP during exercise has been found to predict hypertension (Singh JP, et al, 1999, Allison TG et al 1999, Manolio TA et al 1994, Goble MM and Schieken RM 1991), coronary heart disease (Mundal R et al 1996, McHam SA et al 1999), and CVD death (Lauer MS et al 1995, Filipovsky J et al 1992, Mundal R et al 1994). However, an exercise SBP measurement has had only limited value in the evaluation of cardiovascular risk in hypertensive men compared to measurement of resting SBP (Fagard R et al 1991). Physical capacity may have an effect on the SBP rise, because maximum exercise capacity varies among individuals.

Elevated SBP immediately after exercise may also reflect the overactivity of sympathetic nervous system and attenuated vagal reactivation (Cole CR et al 1999). During graded exercise, both the heart rate and SBP progressively increase, owing to an increase in activity of the sympathetic nervous system with a concomitant decrease in the parasympathetic activity (Frolkis JP et al 2003). Gradual decrease of SBP after exercise may be due to the autonomic dysfunction and vasoreactivity abnormalities (Singh JP et al 1999, Lim PO et al 1996). 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 (Dimsdale JE et al 1984). Sympathetic activation during the anticipation phase of exercise is manifested as an increase in cardiac output with no compensatory decrease in vascular resistance (Everson SA et al 1996). SBP may remain elevated for a longer time

if sympathetic tone does not decrease and vagal tone does not increase during the postexercise period (Davidoff R et al 1982, Pescatello LS et al 1991, Hashimoto M et al 1993, Palatini P 1998).

The present study shows that SBP during the recovery period may provide an additional risk marker for identifying asymptomatic individuals at an increased risk for acute stroke. In the present study, an impaired fall from maximum SBP to recovery markedly increased the risk of any stroke. Percentage of SBP at two minutes after exercise of the maximal SBP indicated that SBP remains elevated during recovery from the maximum value, which may indicate increased systemic vascular resistance. Therefore, it could be useful to measure SBP after exercise to detect men at high risk for future strokes.

6.4 Silent myocardial ischemia and the risk of stroke

In the present study, men with silent myocardial ischemia had a substantially increased risk for stroke and CVD death if they had any of several other common risk factors. Painless myocardial ischemia during exercise in the presence of at least one of the conventional risk factors including smoking, hypercholesterolemia, hypertension and overweight, helps to identify individuals who may benefit from intensive risk factor reduction. Ischemic ST-segment changes during exercise are considered a marker of myocardial ischemia due to underlying coronary atherosclerosis. It is also possible that myocardial ischemic ST-segment changes may indicate an increased risk of other CVDs because of generalized atherosclerosis. Furthermore, ischemic ST-segment changes in the presence of common risk factors, such as hypertension, smoking, hypercholesterolemia, and overweight may increase the probability of CHD, as well as other atherosclerotic CVDs. However,

there are no previous population-based studies exploring whether silent, exercise-induced, ST-segment depression predicts the risk of CVDs and cerebrovascular diseases in high-risk individuals.

In the present study, men with silent myocardial ischemia had a substantially increased risk for stroke and CVD death if they had any of several other common risk factors. It is plausible that silent myocardial ischemia on ECG testing is a reflection of advanced atherosclerosis, not only in the coronary arteries but also in large arteries of the cerebral circulation (Chua HC et al 1999, Keys A 1980). Because atherosclerosis is the pathological basis of occlusive cerebrovascular disease, it may partly explain the association between exercise-induced myocardial ischemia and stroke. CHD and stroke share several risk factors, and an association between atherosclerotic cerebrovascular disease and CHD has been established in several studies (Miranda CP et al 1991, Chua HC et al 1999, Lakka TA et al 1994). This may partially explain the association between exercise-related silent myocardial ischemia and stroke found in high-risk individuals in the present study. Our results are in line with the recommendations that asymptomatic, high-risk individuals with any of the major coronary risk factors should undergo ECG testing to better define their risk for CHD (Deedwania PC and Nelson JR 1990, Smith SC Jr et al 2000).

6.5 Cardiorespiratory fitness and risk of stroke

It has been shown that exercise capacity is a more powerful predictor than many other common clinical and exercise test variables (Myers J et al 2002). Good exercise capacity is a strong predictor of mortality in men with history of hypertension, chronic obstructive pulmonary disease, diabetes, smoking, obesity or elevated serum total cholesterol levels as well as in subjects with or

without underlying CVD or the use of ß-blockers (Myers J et al 2002).

The expert panel suggested that every U.S. adult should exercise 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 (Pate RR et al 1995, Johnson JM and Ballin SD 1996). A randomized trial (Dunn AL et al 1999), showed 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 (Dunn AL et al 1999). In a previous study, authors reported a nearly linear reduction in mortality as fitness levels increased, and each increase of 1 MET in exercise capacity conferred a 12 percent improvement in survival among men referred exercise testing for clinical reasons (Myers J et al 2002). This prospective population-based study among middle-aged men used VO_{2max} as a measure of cardiorespiratory fitness showed a strong and inverse association of VO_{2max} with stroke. In fact, VO_{2max} was one of the strongest predictors for stroke in our present unselected Finnish middle-aged cohort. These findings are consistent with U.S. cohort studies (Myers J et al 2002, Blair SN et al 1996, Wei M et al 1999), suggesting that the risk of mortality associated with low cardiorespiratory fitness is comparable with that of conventional risk factors including hypertension, smoking, obesity hypercholesterolemia and diabetes.

The optimal intensity of exercise and the level of cardiorespiratory fitness recommended for the subjects with atherosclerotic diseases should be defined individually.

6.6 Exercise cardiac power and risk of stroke

Cardiac power, an easily available novel marker of peak cardiac output during exercise, was associated with an increased risk of incident stroke in a population-based study of men from eastern Finland. The integration of afterload while using peak SBP and VO_{2max} increases emphasis on the role of ergospirometry and gives prognostic information in addition to that obtained by conventional methods. ECP takes into consideration not only the preload but also afterload that potentially increases its value as a prognostic marker for stroke. VO_{2max} may be preserved among subjects with medications lowering afterload despite the reduced pumping capacity. Antihypertensive medication may decrease the afterload and increase cardiac output to a higher level during progressive exercise. In addition, subjects who are inactive and sedentary may present with a considerably reduced VO_{2max}. Furthermore, our study showed that ECP was an important predictive factor among men on antihypertensive medication. Because ECP is a function of cardiac output (VO_{2max}) and peripheral resistance (SBP), it may improve the predictive value of VO_{2max} alone. Cardiac power during exercise may provide additional valuable information on the evaluation of stroke risk.

7 SUMMARY AND CONCLUSIONS

1. Blood pressure observation during and after the exercise stress test provides valuable information the prevention of not only for cardiac diseases but also for stroke. Systolic blood pressure response during an exercise test provides noninvasive means in identifying individuals at an increased risk for future strokes.

2. Silent myocardial ischemia during and after exercise stress test, as indicated by ST depression in ECG, predicts stroke in the presence of common conventional risk factors in men clinically free of CHD. Silent myocardial ischemia during exercise testing is important in identifying high risk individuals who would benefit most of preventive measures.

3. Cardiorespiratory fitness is one of the strongest risk predictors of stroke emphasizing the importance of exercise testing in clinical practise. Cardiorespiratory fitness provides valuable information in individuals withcardiovascular risk factors, and is comparable to smoking, dyslipidemia, hypertension, diabetes and obesity as arisk factor for stroke.

4. Exercise Cardiac power, an easily available novel marker of peak cardiac output during exercise, is an important predictor of stroke risk. The integration of afterload while using peak SBP and VO_{2max} increases emphasis on the role of ergospirometry and gives prognostic information in addition to that obtained by conventional methods.

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Exercise Stress Test in Stroke Risk Prediction

Stroke is the leading cause of morbidity and the third-leading cause of mortality after ischaemic heart disease and cancer. Stroke remains a major healthcare problem, and it is the most common neurological reason for hospitalization. Although we have made great strides in the diagnosis and treatment of stroke, the overall incidence of stroke will continue to rise as our population ages. It is estimated that 14,000 strokes occur in Finland each year. Primary prevention of stroke is of vital importance because over 70% of the strokes are first events.

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