Association of Exercise-Induced, Silent ST-Segment Depression With the Risk of Stroke and Cardiovascular Diseases in Men

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Background and Purpose—There are few if any data on the prognostic importance of silent myocardial ischemia during exercise with regard to the risk of stroke and cardiovascular diseases (CVDs) among asymptomatic men. In this prospective study, we investigated the relation of silent myocardial ischemia and the risk of stroke and CVD death in men with and without conventional risk factors.

Methods—The study sample included 1726 middle-aged men with no history of stroke, coronary heart disease, or atrial fibrillation at baseline. Silent myocardial ischemia was defined as a horizontal or downsloping ST-segment depression ($\geq 1$ mm) during exercise electrocardiography. A total of 86 CVD-related deaths and 78 strokes occurred during an average follow-up of 10 years.

Results—Men with silent ischemia during exercise had a 3.5-fold increased risk of CVD death and 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% confidence interval [CI], 1.5 to 9.5) increased risk for CVD in smokers, a 3.9-fold (95% CI, 2.1 to 7.3) increased risk in hypercholesterolemic subjects, a 3.6-fold (95% CI, 1.9 to 6.8) increased risk in the hypertensives, and 3.8-fold (95% CI, 2.0 to 7.1) increased risk in overweight men. The respective relative risks for stroke were 3.8 (95% CI, 1.1 to 12.5), 3.5 (95% CI, 1.7 to 7.4), 3.4 (95% CI, 1.6 to 7.1), and 2.9 (95% CI, 1.4 to 6.1).

Conclusions—Exercise-induced silent myocardial ischemia is an important indicator of increased risk of stroke and CVD in men with other risk factors, such as smoking, hypercholesterolemia, hypertension, and being overweight. (Stroke. 2003;34:1760-1765.)

Key Words: cardiovascular diseases ■ risk factors ■ silent ischemia ■ stroke, cardioembolic

Previous studies have shown that exercise-induced myocardial ischemia increases the risk of future coronary events in both patients with coronary heart disease (CHD) and asymptomatic individuals with no prior CHD. There are, however, few if any data demonstrating that silent ischemia during or after exercise has a long-term prognostic significance with regard to stroke and cardiovascular disease (CVD) death. 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. Little is known about the prognostic value of exercise-induced silent myocardial ischemia in high- and low-risk individuals, however.

Some evidence shows that electrocardiographic (ECG) findings may predict the risk of stroke. The exercise test is commonly used to screen both men $>45$ and women $>55$ years of age with suspected CHD. 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.
The aim of the present study was to investigate the prognostic significance of silent myocardial ischemia during an exercise test with regard to the risk of any CVD death and stroke in a population-based sample of asymptomatic men. Additionally, we investigated whether hypertension, overweight, serum LDL cholesterol level, and smoking modify these associations in men with no prior stroke or CHD.

Methods

Subjects

Subjects were participants in the Kuopio Ischemic Heart Disease Risk Factor Study, an ongoing, population-based study designed to investigate risk factors for CVD, atherosclerosis, and related outcomes in men from eastern Finland, an area of high coronary morbidity and mortality.13 Each subject gave written, informed consent. The Research Ethics Committee of the University of Kuopio approved the Kuopio Ischemic Heart Disease Risk Factor Study. The baseline examinations were conducted between March 1984 and December 1989. The subjects were a random sample of men aged 42, 48, 54, or 60 years at the baseline examination. Of 3235 eligible men, 2682 (82.9%) participated in the study.

Exercise Tolerance Test

A maximal, symptom-limited, exercise stress test was performed with an electrically braked bicycle ergometer between 8 AM and 12 noon. The testing protocol comprised a 3-minute warm-up at 50 W followed by a step-by-step increase in the workload by 20 W/min (Tunturi EL 400 bicycle ergometer) for 407 (23%) men. The remaining 1362 men (77%) were tested with a linear increase in the workload of 20 W/min (Medical Fitness Equipment 400 L bicycle ergometer). Maximal oxygen uptake was measured directly with a respiratory gas analyzer, as explained previously.15 Also, heart rate and blood pressure were registered during the exercise test. Blunted heart rate response was defined as inability to achieve 85% of the age-predicted, maximal heart rate during exercise.

The most common reasons for stopping the exercise test early were exhaustion (1235 men), breathlessness (229 men), and pain in the leg, joints, or back (n=69). The test was discontinued because of cardiopulmonary symptoms or abnormalities for 120 men. These included arrhythmias (n=51), a marked change in systolic (SBP) or diastolic blood pressure (n=35), dizziness (n=8), or ischemic ECG changes (n=6). Exercise-induced, ventricular conduction disorders were observed in 4 men, 1 of whom also had silent myocardial ischemia during exercise.

Assessment of Exercise-Induced Myocardial Ischemia

The ECG was recorded continuously with a Kone 620 ECG. The Mason-Likar lead system, including V1, V5, and aVF lead connections, was used.16 The ECG was printed out at 30-second intervals during exercise and for at least 5 minutes of recovery while the subject was sitting on the bicycle. Exercise ECGs were coded manually by 1 cardiologist (J.E.). Silent myocardial ischemia during exercise and afterward was defined as ischemia in the ECG without typical chest pain indicating CHD. The criteria for ischemia on the ECG during exercise were horizontal or downsloping ST-segment depressions ≥1.0 mm at 80 ms after the J-point or any ST-segment depression ≥1.0 mm at 80 ms after the J-point.

Ascertainment of Strokes and CVD Death

Incident strokes between 1984 and 1992 were ascertained through the FINMONICA stroke register.17 Information on stroke incidence between 1993 and December 31, 1998 was obtained by computerized linkage to the Finnish national hospital discharge registry and death certificate registry. Diagnostic information was collected from hospitals and classified by 1 neurologist (J.S.) using diagnostic criteria identical to the FINMONICA criteria. The sources of information on stroke were from hospital documents, death certificates, autopsy reports, and medicolegal reports. The diagnosis of stroke was based on the sudden onset of clinical signs or focal or global disturbance of cerebral function lasting >24 hours (except in the case of sudden death or when interrupted by surgical intervention) with no apparent cause other than a vascular origin. Each suspected stroke (ICD-9 codes 430 to 439 and ICD-10 codes I60-I68 and G45-G46) was classified as (1) definite stroke, (2) no stroke, or (3) an unclassifiable event. The data from the FINMONICA stroke register 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 as (1) an ischemic stroke (ICD-9 codes 433 to 434 or ICD-10 code I63) or (2) a hemorrhagic stroke (ICD-9 codes 430 to 431 or ICD-10 codes I60-I61). If the subject had multiple nonfatal strokes during follow-up, the first stroke was considered the end point. The average follow-up time was 10.4 years (range, 0.3 to 13.4 years). A total of 78 first strokes occurred, of which 59 were ischemic strokes. In the present sample, there were 86 CVD deaths (ICD-9 and ICD-10 codes 390 to 459 and I00-I09, respectively), 60 of which were due to CHD and 19 due to stroke.

Assessment of Other Risk Factors

The examination protocol and the assessment of medical history, use of medications, smoking habit, alcohol consumption, blood pressure, and body mass index (BMI) have been described in detail previously.18,19 Hypertension was defined as SBP >140 mm Hg, diastolic blood pressure >90 mm Hg, or the use of antihypertensive medication. BMI was computed as the ratio of weight in kilograms divided by the square of height in meters. The collection of blood specimens and the measurement of serum lipids have been presented previously elsewhere.18,19

Statistical Methods

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 (1985, 1986, 1987, 1988, and 1989) and the well-known risk factors (smoking habit, 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 (≥3.5 mmol/L) and lower (<3.5 mmol/L) serum LDL cholesterol levels, (3) hypertensive and normotensive men, and (4) overweight to obese (≥25 kg/m²) men and normal-weight (<25 kg/m²) men. Statistical tests for significance were 2-sided, and analyses were performed with SPSS, version 10.0, for Windows.

Results

Baseline Characteristics

Baseline characteristics in men with and without myocardial ischemia during exercise are shown in Table 1. Serum LDL...
The strongest risk factors for stroke were elevated SBP (P<0.001) and silent ischemic ST-segment depression during exercise (P=0.02). The strongest risk factors for CVD death were smoking (P<0.001), elevated SBP (P<0.001), silent ischemic ST-segment depression during exercise (P<0.001), and alcohol consumption (P=0.02). In these multivariate models, blunted heart rate response and maximal oxygen uptake were not related to the risk of stroke, whereas the later was inversely related to the risk of CVD death (P=0.03).

### Prevalence of Silent Myocardial Ischemia at Baseline

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. The number of men with reasons other than silent ischemia for having an abnormal exercise test were 78 (including severe arrhythmias, no increase in SBP, and painful ischemia).

### Number of Strokes and CVD Deaths During Follow-Up

Seventeen (13.8%, P<0.05) of 123 men with silent ischemia during exercise and 69 (4.3%, P<0.05) of 1603 men without silent ischemia died of CVD during follow-up. The respective numbers (percentages) for stroke were 10 (8.1%) and 68 (4.2%). A total of 9 men had both an acute coronary event and a stroke, of whom 2 had the acute coronary event before stroke during the follow-up.

### Strongest CVD Risk Factors

The strongest risk factors for stroke were elevated SBP (P<0.001) and silent ischemic ST-segment depression during exercise (P=0.02). The strongest risk factors for CVD death were smoking (P<0.001), elevated SBP (P<0.001), silent ischemia during exercise (P=0.001), and alcohol consumption (P=0.02). In these multivariate models, blunted heart rate response and maximal oxygen uptake were not related to the risk of stroke, whereas the later was inversely related to the risk of CVD death (P=0.03).

### Relative Risk of Stroke and CVD Death in Men With Silent Myocardial Ischemia

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 (Table 2). 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 (Figures 1 and 2). 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 (relative risk [RR]=3.0; 95% confidence interval [CI], 1.5 to 6.0, P=0.001).

### Interactions of Silent Ischemia With Conventional CVD 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 (Figure 3a and 3b). 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 hypertensives (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 risks of stroke were RR=3.8; 95% CI, 1.1 to
12.5 in smokers; RR=3.5; 95% CI, 1.7 to 7.4 in hypercholesterolemic men; and RR=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 RRs for CVD death were a 3.2-fold (95% CI, 1.7 to 6.0) increased risk for men with hypertension and hypercholesterolemia, a 4.1-fold (95% CI, 1.9 to 9.0) increased risk for smokers with hypercholesterolemia, and a 8.4-fold (95% CI, 4.3 to 16.4) increased risk for smokers with hypertension. In men with silent ischemia and the presence of 3 conventional risk factors (hypertension, hypercholesterolemia, and smoking), the RRs were a 4.9-fold (95% CI, 1.51 to 15.9) increased risk for stroke and 5.8-fold (95% CI, 2.3 to 14.7) increased risk for CVD death. 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 significant 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.

**Discussion**

This prospective, population-based study demonstrates that silent myocardial ischemia during exercise, as indicated by painless ST-segment depression on the ECG, is associated with an increased risk of stroke and CVD death in asymptomatic, middle-aged men who have additional risk factors, such as smoking, hypercholesterolemia, hypertension, and being overweight.

The prognostic value of silent myocardial ischemia, as indicated by exercise ECG findings, varies considerably in previous studies, most likely because of different selection criteria for the subjects. Most studies have included only patients with CHD, whereas few studies have included persons without prior CHD. It has been argued...
that the prognostic value of exercise ECG is low in totally asymptomatic persons because of false-positive and false-negative responders. However, in healthy individuals with a high pretest probability of CHD, eg, in those with major CVD risk factors, the frequency of false-positive test responses for myocardial ischemia is lower than in those without coronary risk factors, which diminishes the bias associated with false-positive responders (the Bayes’ rule). This is consistent with our results showing that the association between silent myocardial ischemia with stroke and CVD risk was stronger in high- than in low-risk groups. This finding is in accordance with the approach of Diamond and Forrester, which demonstrated the role of other risk factors in modifying the likelihood of future CVD among patients with or without atypical angina.

It has been suggested that risk assessment for primary CHD is enhanced by detection of abnormal exercise ECG findings only in those who have 1 or more conventional risk factors. 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 any 1 of these risk factors (smoking, hypercholesterolemia, hypertension, or overweight) helps to identify individuals who may benefit from intensive risk factor reduction. 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.

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. 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.\textsuperscript{3-12,15} This may partially explain the association between exercise-related silent myocardial ischemia and stroke found in high-risk individuals in the present study.

The use of a small, ST-segment depression as a diagnostic criterion can decrease the test’s specificity because conditions other than myocardial ischemia, such as hyperventilation, electrolyte abnormalities, anemia, ventricular hypertrophy, and increased sympathetic activity, are known to cause ST-segment depression.\textsuperscript{9,19} One limitation of the present study is that we studied only middle-aged men, and thus, our findings may be not generalized to elderly and female populations. Furthermore, exercise ECG testing is generally used as an initial screening test that is followed by more accurate methods, such as pharmacological echocardiography, myocardial perfusion imaging, positron emission tomography, and ambulatory ECG monitoring, and assessment of the arteries by ultrasonography or magnetic resonance imaging.\textsuperscript{22,26,27} Our data do not address how frequently the patients identified with silent ischemic changes on exercise ECG would benefit from these other tests.

In conclusion, our results do not support generalized screening of low-risk populations with exercise ECG testing. However, the finding of silent myocardial ischemia on exercise testing in high-risk, asymptomatic men may help to identify a subgroup at particularly high risk of stroke and CVD death who may benefit from further evaluation and intensive risk factor modification. Whether this would translate into improved health outcomes requires further study.

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