Cardiac Power During Exercise and the Risk of Stroke in Men

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Background and Purpose—Low maximal oxygen uptake (VO2max) has been shown to predict the risk of stroke. However, VO2max does not take into account the differences in cardiac afterload between subjects. The aim of this study was to examine the relationship of exercise cardiac power (ECP), defined as a ratio of VO2max with peak systolic blood pressure (SBP) during exercise, with the risk for stroke.

Methods—Population-based cohort study with an average follow-up of 12 years from eastern Finland. A total of 1761 men with no history of stroke or coronary heart disease at baseline participated. Among these men, 91 strokes occurred, of which 69 were attributable to ischemic causes.

Results—The relative risk of any stroke in men with low ECP (<10.3 mL/mm Hg) was 2.7 (95% CI, 1.2 to 6.0; P=0.01; P=0.02 for the trend across the quartiles), and the relative risk for ischemic stroke was 2.7 (95% CI, 1.1 to 7.0; P=0.03; P=0.04 for trend across the quartiles) compared with men having high ECP (>14.3 mL/mm Hg) during exercise after adjusting for age, examination year, cigarette smoking, alcohol consumption, body mass index, diabetes, serum total cholesterol level, energy expenditure of physical activity, exercise-induced myocardial ischemia, and the use of antihypertensive medication. After further adjustment for resting SBP, results were statistically nonsignificant.

Conclusions—Low ECP provides noninvasive and easily available measure for stroke risk. One of the most potential explanations for the association between ECP and the increased risk of stroke is an elevated afterload and peripheral resistance indicated by elevated SBP. (Stroke. 2005;36:820-824.)

Key Words: blood pressure ■ epidemiology ■ risk factors ■ stroke ■ stroke, ischemic

Previous studies have shown that good cardiorespiratory fitness has protective effects on atherosclerotic cardiovascular diseases, including coronary heart diseases (CHDs), hypertension, and stroke.1–4 Good cardiorespiratory fitness and physical activity may reduce the risk of stroke by affecting modifiable risk factors, including hypertension,5 obesity,6 and dyslipidemia.7 Cardiorespiratory fitness, when measured by maximal oxygen uptake (VO2max) during exercise, has been shown to have a strong inverse relation to the risk of stroke.8 It has been proposed that measurement of VO2max should be included when clinical decisions are being made in patients referred for evaluation of cardiovascular diseases (CVDs). Although VO2max 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. Systolic blood pressure (SBP) at rest is a well-established risk factor for stroke. In addition to resting SBP, exercise-induced elevation of SBP has been found to be an independent predictor of stroke.9 Hypertension,10–14 CHD,15,16 and CVD17–19 death.

Systolic blood pressure (SBP) at peak exercise and VO2max are the 2 variables that are useful in stroke risk stratifying for stroke. Therefore, we hypothesized that an index of exercise cardiac power (ECP) defined as the ratio of VO2max with peak SBP gives prognostic information beyond that obtained by using either of these risk factors alone in stroke risk stratification. Therefore, we investigated the association of ECP by integrating surrogates of preload (VO2max) and afterload (SBP) during exercise with the risk of stroke in a population-based sample of men from eastern Finland.

Methods

Subjects

Subjects were participants in the Kuopio Ischemic Heart Disease Risk Factor Study (KIHD), designed to investigate risk factors for CVD, carotid atherosclerosis, and related outcomes in a population-based, randomly selected sample of men from eastern Finland.20 Of the 3433 men aged 42, 48, 54, or 60 years who resided in the town of Kuopio or its surrounding rural communities, 198 were excluded because of death, serious disease, or migration away from the area. At baseline, examinations were conducted on 2682 men (82.9% of

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the potential eligible) between March 1984 and December 1989. Men who had a history of stroke (69 men) or history of CHD (677) were excluded from the study. Complete data were available on 1761 subjects with no history of stroke or CHD at baseline in this study.

Assessment of Exercise Cardiac Pumping Capacity

VO_{2max} was defined directly from respiratory gases during exercise test, and SBP was measured during a standardized exercise test. Oxygen consumption and SBP were assessed with a maximal symptom-limited exercise-tolerance test on an electrically braked bicycle ergometer. All the men underwent the testing protocol using a step-by-step increase in the workload by 20 W per minute.

A detailed description of the measurement of VO_{2max} has been given previously. In short, respiratory–gas exchange was measured for the first 614 men by the mixing-chamber method, and for the rest, 1698 men by a breath-by-breath method. VO_{2max} was defined as the highest value for, or the plateau on, oxygen uptake. Blood pressure was measured every 2 minutes manually and automatically during the exercise until the test was stopped and every 2 minutes after exercise. The highest SBP achieved during the exercise test was defined as the maximal exercise SBP (peak SBP). Blood pressure was also measured during recovery after the exercise at regular intervals of 2, 4, 6, and 8 minutes sitting on the bicycle. ECP was defined as VO_{2max} divided by maximal SBP during exercise. Resting blood pressure was obtained by the same experienced nurse using a random-zero sphygmomanometer after 5 and 10 minutes of rest in the seated position. The mean of these 2 values was used as resting blood pressure. ECG was registered continuously during the exercise stress test.

Assessment of Other Covariates

Assessment of smoking, alcohol consumption, and blood pressure was performed as described previously. Body mass index (BMI) was computed as the ratio of weight (kilograms) to the square of height (meters). The collection of blood specimens and the measurement of serum lipids have been described previously.

Ascertainment of Follow-up Events or Stroke

Incident strokes between 1984 and 1992 were ascertained through the Finnish part of Monitoring of Trends and Determinants in Cardiovascular Diseases (FINMONICA) stroke register. 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 (J.S.) with diagnostic criteria identical to the FINMONICA criteria. The sources of information on stroke were hospital documents, death certificates, autopsy reports, and medicolegal 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 ischemic stroke (ICD-9 codes 433 to 434, ICD-10 code I63) or (2) a hemorrhagic 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 report were stored by 100% by 1997. The average follow-up time was 12 years (range 0.2 to 14.8 years). A total of 91 first strokes occurred, of which 69 were ischemic.

Statistical Analysis

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 year, 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 low-density lipoprotein (LDL) cholesterol. To show the independent relationship between ECP and risk of stroke, resting SBP was included in model 2.

The inter-relations between other conventional risk factors and the risk of stroke were analyzed in Cox model entering SBP, BMI, alcohol consumption, and serum LDL cholesterol as quartiles except for smoking (yes or no), with age and examination years adjusted into models. Relative hazards, adjusted for risk factors, were estimated as antigammas of coefficients from multivariate models. All tests for statistical significance were 2 sided. The fit of the proportional hazards models was examined by plotting the hazard functions in different categories of risk factors over time. All statistical analyses were performed using the SPSS 10.0 Windows software.

Results

Baseline Characteristics

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, they smoked more, had higher serum LDL cholesterol, SBP, and diastolic blood pressure, higher prevalence of diabetes, and were less active physically and consumed more alcohol compared with those who had higher ECP (Table 1).

Risk Predictors for Stroke

As continuous variables, the strongest statistically significant risk factors for any stroke were resting SBP (P<0.001), ECP (P=0.002), BMI (P=0.002), diabetes (P=0.007), use of antihypertensive medication (P=0.04), and smoking (P=0.05), after adjustment for age and examination years. The respective risk factors as continuous variables for ischemic stroke were resting SBP (P<0.001), BMI (P=0.002), diabetes (P=0.008), and ECP (P=0.01). An SD increase in ECP (3.08 mL/mm Hg) was associated with a decreased risk of any stroke by 32% (95% CI, 47% to 12%) and ischemic stroke by 31% (95% CI, 48% to 8%). An SD increase in VO_{2max} (539.7 mL/min) was not associated with a decreased risk of any stroke (relative risk [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 (model 2). 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) and ischemic stroke (RR, 1.1; 95% CI, 0.90 to 1.40; P=0.402), respectively.

Maximal Cardiac Power and Risk for Any Stroke in Healthy Men

ECP was related inversely to the risk of stroke (Table 2). Men with 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
TABLE 2. The RR of Stroke in the Quarters of Maximal Cardiac Power (ECP) in Men With No History of Stroke CHD at Baseline.*

<table>
<thead>
<tr>
<th>Maximal Cardiac Power (mL/mm Hg)</th>
<th>Any Stroke (n=91)</th>
<th>Ischemic Stroke (n=69)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR (95% CI)*</td>
<td>P Value</td>
</tr>
</tbody>
</table>
| 0.01 for linear trend across the quarters). Low ECP was associated with a 2.7-fold risk of any stroke after additional adjustment for 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.

Low ECP was also associated with a 2.9-fold risk of ischemic stroke after adjusting for age and examination years and with a 2.7-fold risk of ischemic stroke after further adjustment for 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.

**TABLE 1. Characteristics of Men With No History of Stroke or CHD at Baseline in the Quarters (Q) of Maximal Cardiac Power**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>52.2 (5.3)</td>
<td>49.6 (5.3)</td>
<td>51.9 (5.1)</td>
<td>52.8 (5.1)</td>
<td>＜0.001</td>
</tr>
<tr>
<td>Cigarette smoking (pack y)*</td>
<td>7.6 (15.6)</td>
<td>5.5 (12.3)</td>
<td>4.8 (12.2)</td>
<td>8.0 (15.1)</td>
<td>＜0.001</td>
</tr>
<tr>
<td>Serum LDL cholesterol (mmol/L)</td>
<td>4.01 (0.98)</td>
<td>3.83 (0.91)</td>
<td>3.93 (0.95)</td>
<td>4.14 (0.99)</td>
<td>＜0.001</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>134.1 (16.3)</td>
<td>127.6 (13.0)</td>
<td>131.9 (14.4)</td>
<td>135.1 (14.6)</td>
<td>＜0.001</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>89.1 (10.4)</td>
<td>85.7 (9.0)</td>
<td>88.7 (10.1)</td>
<td>89.8 (9.8)</td>
<td>＜0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.6 (3.4)</td>
<td>26.8 (3.3)</td>
<td>26.8 (3.4)</td>
<td>26.8 (3.2)</td>
<td>＜0.001</td>
</tr>
<tr>
<td>Leisure-time physical activity (kcal/week)</td>
<td>969.8 (1185.7)</td>
<td>1246.6 (1264.3)</td>
<td>1073.4 (1445.5)</td>
<td>791.2 (941.3)</td>
<td>＜0.001</td>
</tr>
<tr>
<td>Alcohol consumption (g/week)</td>
<td>72.7 (110.9)</td>
<td>70.9 (103.7)</td>
<td>69.3 (99.4)</td>
<td>73.9 (117.0)</td>
<td>＜0.001</td>
</tr>
</tbody>
</table>

Q1, ＞14.32 mL/mm Hg; Q2, 12.22–14.32 mL/mm Hg; Q3, 10.29–12.21 mL/mm Hg; Q4, ＞10.92 mL/mm Hg (quarters).

*Pack y denotes the lifelong exposure to smoking that was estimated as a product of years smoked and the No. of tobacco products smoked daily at the time of examination.

LTPA indicates leisure time physical activity.

Maximal Cardiac Power and Risk of Ischemic Stroke

Low ECP was also associated with an increased risk of ischemic stroke (Table 2). Men with low ECP had a 2.9-fold risk of ischemic 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 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.
exercise-induced myocardial ischemia, and serum LDL cholesterol (Table 2). After additional adjustment for resting SBP, the men with low ECP had a 2.27-fold (95% CI, 0.89 to 5.78; $P=0.08$) risk for ischemic stroke.

Maximal Cardiac Power, SBP at Rest, and the Risk of Stroke
There was a significant interaction between ECP and resting SBP and the risk of ischemic stroke ($P=0.01$ for the interaction term). Men with low ECP (<13.12 mL/mm Hg, median) with the presence of elevated resting SBP (>132 mm Hg, median) had a markedly increased risk of any and ischemic stroke (Figure 3). Low ECP with elevated resting SBP was related to 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 in the other combinations of ECP and SBP at rest did not differ statistically significantly from the reference group (high ECP and low SBP at rest). Men with low ECP with the presence of high SBP at rest had also a 2.53-fold (95% CI, 1.01 to 5.45; $P=0.04$) increased risk for ischemic stroke.

Discussion
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 VO2max increases emphasis on the role of ergospirometry and gives prognostic information in addition to that obtained by conventional methods.

To the best of our knowledge, this is the first population-based follow-up study showing an association between ECP and the risk for stroke. Our study shows that excessive risk of stroke was observed among men with the lowest level of ECP. A continuous change in ECP (3.1 mL/mm Hg, corresponding to 1 SD) corresponds to 32% decrease in the risk for stroke among these men. In our previous study, an increase in 1 SD change in VO2max (of 3.5 mL/kg per minute) was related to a 17% decrease in the risk for stroke. Therefore, it seems that ECP may be even a stronger predictor for stroke than exercise capacity alone.

VO2max is considered a golden standard for measuring cardiorespiratory fitness. In addition to VO2max, SBP can be measured more reliably during cycle ergometry than with treadmill walking because upper body movements are lessened during the exercise. It has been suggested that VO2max 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 (ie, afterload). Consequently, VO2max may be severely reduced, and thus, it may underestimate cardiac pumping capacity in a large number of subjects. Cardiac output is a descriptor of cardiac function derived from preload, blood pressure, and cardiac output, and ECP takes into consideration not only the preload but also afterload that potentially increases its value as a prognostic marker for stroke.

VO2max 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 VO2max. Furthermore, our study showed that ECP was an important predictive factor among men on antihypertensive medication.
Our previous studies showed that low VO_{2\text{max}} has been associated with accelerated progression of carotid atherosclerosis\textsuperscript{4} and the risk of stroke.\textsuperscript{8} 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.\textsuperscript{21–23} A high intraluminal pressure will lead to extensive change in endothelium and smooth muscle function in intracerebral arteries. In subjects with preclinical atherosclerotic changes and elevated SBP at rest or during exercise, the increased stress on the vessel wall can increase the risk of endothelial injury and permeability over the blood–brain barrier and result in local or multifocal edema.\textsuperscript{24,25} Endothelial damage and change in blood cell–endothelium interaction can lead to local thrombi formation and ischemic lesions. However, in our study, extensive adjustment for known risk factors did not markedly change the association between ECP and risk for stroke, although the adjustment for resting SBP somewhat weakened the observed relationship between ECP and risk for stroke. This emphasizes the role of resting SBP as a well-documented risk factor for stroke.

Because ECP is a function of cardiac output (VO_{2\text{max}}) and peripheral resistance (SBP), it may improve the predictive value of VO_{2\text{max}} alone. Previous studies have suggested that low cardiorespiratory fitness is comparable to other conventional risk factors for CVD.\textsuperscript{10,26} Our findings suggest that it may be useful to assess the level of ECP, although further studies are needed showing the exact value of ECP as a prognostic measure. Given the high cost of treating stroke patients and the limited success of current acute-phase treatments, prevention is the most effective way to decrease the suffering and cost of stroke. The role of ECP can be considered a modifiable risk factor by increasing cardiorespiratory fitness, and a decrease in blood pressure will help in the prevention of stroke risk.

The strengths of this study are that we have a representative population-based sample of middle-aged men with a high participation rate. There were no losses during follow-up. A limitation of this study is that it is based on an ethnically homogenous and middle-aged male population that may limit the generalization of our results. Therefore, more studies are needed in different study populations, especially in elderly and women, to confirm our findings.

This prospective population-based study provides the first evidence that ECP was associated with an increased risk of stroke. Cardiac power during exercise may provide additional valuable information on the evaluation of stroke risk.

References
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