Exercise Capacity and the Risk of Death in Women
The St James Women Take Heart Project
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Background—Cardiovascular disease is the leading cause of death among women and accounts for more than half of their deaths. Women have been underrepresented in most studies of cardiovascular disease. Reduced physical fitness has been shown to increase the risk of death in men. Exercise capacity measured by exercise stress test is an objective measure of physical fitness. The hypothesis that reduced exercise capacity is associated with an increased risk of death was investigated in a cohort of 5721 asymptomatic women who underwent baseline examinations in 1992.

Methods and Results—Information collected at baseline included medical and family history, demographic characteristics, physical examination, and symptom-limited stress ECG, using the Bruce protocol. Exercise capacity was measured in metabolic equivalents (MET). Nonfasting blood was analyzed at baseline. A National Death Index search was performed to identify all-cause death and date of death up to the end of 2000. The mean age of participants at baseline was 52±11 years. Framingham Risk Score–adjusted hazards ratios (with 95% CI) of death associated with MET levels of ≤5, 5 to 8, and >8 were 3.1 (2.0 to 4.7), 1.9 (1.3 to 2.9), and 1.00, respectively. The Framingham Risk Score–adjusted mortality risk decreased by 17% for every 1-MET increase.

Conclusions—This is the largest cohort of asymptomatic women studied in this context over the longest period of follow-up. This study confirms that exercise capacity is an independent predictor of death in asymptomatic women, greater than what has been previously established among men. The implications for clinical practice and health care policy are far reaching. (Circulation. 2003;108:1554-1559.)

Key Words: exercise ■ epidemiology ■ mortality ■ women

Coronary artery disease (CAD) is the leading cause of death in both men and women in the United States. Women differ from men in their clinical presentation of CAD, their performance on diagnostic tests, and their prevalence of CAD. However, most of the available data on the noninvasive diagnosis of CAD are based on studies in men. Because the pretest likelihood of CAD, referral patterns and diagnostic ability of available tests probably differ for women, the clinical evaluation of women is difficult.1,2

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The standard exercise ECG is the most commonly used and the least costly noninvasive test to identify CAD. The value of the exercise ECG comes from the wealth of information that can be extracted from the test to provide important prognostic and diagnostic information.3 Epidemiologic studies have noted that exercise capacity is an independent predictor of cardiovascular events and all-cause death in men.4–11 Most studies examining the predictive value of exercise capacity have included almost exclusively male subjects4,5,7,8,10,11 or were retrospective studies.12 Also, most studies examining exercise capacity included only subjects with established CAD or cardiac symptoms.5,6,11–14 A prior study that included asymptomatic women showed an association between exercise capacity and death, but their extensive exclusion criteria limit the generalizability of their findings.15 Previous research has not evaluated all potential prognostic indicators from stress tests in asymptomatic women; therefore, the American College of Cardiology (ACC)/American Heart Association (AHA) Committee on Exercise Testing has identified this as an area in need of further study.3

In this study, we assess the prognostic value of exercise capacity in asymptomatic women. The aim of this paper is to determine whether exercise capacity is an independent predictor for all-cause death in asymptomatic women.
Methods

This study was approved by St James Hospital and Rush-Presbyterian-St Luke’s Medical Center’s Institutional Review Board.

Participants

The St James Women Take Heart (WTH) Project comprises a volunteer cohort of women from the greater Chicago metropolitan area who responded to advertisements on television news and print media to participate in a study of heart disease in women during 1992. The target study enrollment was 5000. Inclusion criteria were age 35 years or older, a lack of symptomatic CAD, and the ability to walk on a treadmill at a moderate pace. Women were excluded if they had had typical anginal symptoms or myocardial infarction within the previous 3 months, had blood pressures of ≥170/110 mm Hg before initiating the stress test, weighed >325 pounds (because of equipment limitations), or were pregnant; 5932 women met the inclusion criteria and were examined between May and July of 1992.

Our study-specific exclusion criteria excluded those who underwent a modified Bruce protocol stress test (n = 109), because submaximal exercise testing does not accurately reflect physical fitness in the way that maximal exercise testing does.16 Women with self-reported CAD, previous percutaneous coronary angioplasty, coronary artery bypass graft, or congestive heart failure were also excluded from this analysis (n = 91). We excluded 11 women because of incomplete data concerning cardiac risk factors.

After obtaining informed consent, participants provided data on demographics, lifestyle, behavioral variables, and medical history by self-administered questionnaire. Registered nurses performed physical examinations, which included height, weight, waist and hip measurements, blood pressure, radial pulse rate, and auscultation of the heart and lungs. Body mass index was calculated as weight in kilograms divided by height in meters squared. Blood pressure was measured by standard clinical procedures.17 Random urine and nonfasting blood samples were collected for laboratory analysis. Findings suggestive of congestive heart failure, valvular disease, or peripheral vascular disease were referred to the attending cardiologist. During the recording of the resting ECG, supine blood pressures were measured by cardiac technicians. Standing blood pressures were recorded before the stress test.

Framingham Risk Score

The Framingham Risk Score (FRS) has been described previously.18 The scoring for women is calculated by using a point system for total cholesterol, HDL, age, systolic blood pressure, diastolic blood pressure, the presence or absence of diabetes mellitus, and current smoking. The score ranges between −17 and +25, with higher scores indicating more cardiac risk factors.

We defined diabetes as either self-reported diabetes or nonfasting glucose level of ≥11 mmol/L.19

Exercise Testing

Participants underwent a symptom-limited treadmill test according to the Bruce protocol with exercise ECG measurements.20,21 Heart rate and blood pressure were measured, and a 12-lead ECG was recorded before exercise, at the end of each exercise stage, at peak exercise, and at 1-minute intervals during recovery. The test was discontinued for limiting symptoms (angina, dyspnea, and fatigue), abnormalities of rhythm or blood pressure, or marked and progressive ST-segment deviation. Target heart rates were not used as a predetermined end point.

Exercise capacity is expressed in units of metabolic equivalents (MET) and is an estimate of the maximal oxygen uptake for a given workload.22 A MET is a measure of ventilatory oxygen consumption expressed as multiples of basal resting requirements, where 1 MET is 1 unit of basal oxygen consumption, which equals 3.5 mL oxygen consumption per kilogram of body weight per minute for an average adult. The exercise capacity (in MET) is estimated by the speed and grade of the treadmill.23

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Subjects (n = 5721)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>52.4 ± 10.8</td>
</tr>
<tr>
<td>Race, %</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>85.5</td>
</tr>
<tr>
<td>African American</td>
<td>9.5</td>
</tr>
<tr>
<td>Other*</td>
<td>6</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.4 ± 5.7</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.62 ± 1.07</td>
</tr>
<tr>
<td>HDL, mmol/L</td>
<td>1.35 ± 0.39</td>
</tr>
<tr>
<td>Hypertension†, %</td>
<td>45.1</td>
</tr>
<tr>
<td>Diabetes‡, %</td>
<td>4.9</td>
</tr>
<tr>
<td>Smoking, %</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>79.4</td>
</tr>
<tr>
<td>Current</td>
<td>15.2</td>
</tr>
<tr>
<td>Former</td>
<td>5.4</td>
</tr>
<tr>
<td>FRS, points</td>
<td>6 – 6</td>
</tr>
<tr>
<td>Exercise capacity, MET</td>
<td>8.0 ± 2.7</td>
</tr>
<tr>
<td>Resting heart rate, bpm</td>
<td>79 – 12</td>
</tr>
<tr>
<td>Resting systolic blood pressure, mm Hg</td>
<td>129 – 19</td>
</tr>
<tr>
<td>Resting diastolic blood pressure, mm Hg</td>
<td>82 – 11</td>
</tr>
<tr>
<td>Peak heart rate, bpm</td>
<td>160 – 16</td>
</tr>
<tr>
<td>ST depression ≥1.0 mm, %</td>
<td>6.1</td>
</tr>
</tbody>
</table>

Values are mean ± SD or percentage.

*Other* race category includes those with no stated race.
†Hypertension is defined as history of hypertension or resting systolic blood pressure ≥140 mm Hg or resting diastolic blood pressure ≥90 mm Hg.
‡Diabetes is defined as history of diabetes or nonfasting glucose >11 mmol/L (200 mg/dL).

Follow-Up

All-cause death was used as the end point. Deaths were identified by use of a National Death Index search, matching on date of birth and Social Security number and including all deaths through the year 2000.

Statistical Analyses

Descriptive analyses of all variables were examined. Population characteristics between those who met the primary end point (all-cause death) and the remaining participants were compared by using the χ² test for categorical variables or the t test for continuous variables (2-sided). Exercise capacity (in MET) was modeled as a continuous variable and categorical variable. Exercise capacity was stratified as <5 MET, 5 to 8 MET, or ≥8 MET. This categorization was based on prior studies that showed decreased survival among those who achieved <5 MET and increased survival among those who are able achieve ≥8 MET when estimated either from exercise activities or a stress test.4,12,24

Person-time was calculated for each woman from date of test to date of death from any cause or December 31, 2000, whichever came first. Survival analysis was performed by means of Cox proportional-hazards regression models to determine the effect of exercise capacity on all-cause death, with exercise capacity analyzed as a continuous variable, adjusted for the FRS (as a continuous variable). Analysis of survival within the FRS tertiles for this cohort was performed with the use of the Cox proportional-hazards regression model. Survival was compared by categories of exercise capacity by means of Kaplan-Meier curves. The Cox proportional-hazards assumption was confirmed by visual inspection of the log(−log(survival)) curves. Statistical analyses were performed with the use of STATA 7.0.
During the follow-up period, 3.2% (n/11005) of 5721 women met the inclusion criteria for this analysis. Study population characteristics are given in Table 1. A total of 5721 women were included in the analysis. The mean body mass index was 27.4 (5.7 kg/m²). This was a predominantly white cohort (85.5%); 9.5% were African-American, 4.8% were other, and 2.7% were black. The mean body mass index was 27.4 (5.7 kg/m²). During the follow-up period, 3.2% (n = 180) died. The mean (± SD) survival time was 8.4 ± 0.67 years. The calculated FRS was normally distributed for this population, with a mean FRS of 6.2 ± 6. U. The scores ranged from −12 to 20 U (Figure 1A). Comparing the surviving population with those who died, there was a statistically significant lower FRS in those alive than in those who died (mean FRS, 6.2 ± 6 versus 9 ± 5, P < 0.0001) (Table 2). For each increasing tertile, the FRS predicts the 10-year CAD risk to be 3%, 4% to 8%, and ≥9%, respectively.‡

Table 1. Characteristics of Those Who Survived Compared With Those Who Died

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Survived (n = 5541)</th>
<th>Died (n = 180)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>52.2 ± 10.6</td>
<td>62.3 ± 10.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Race, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>85.4</td>
<td>88.5</td>
<td>0.25</td>
</tr>
<tr>
<td>Other</td>
<td>4.9</td>
<td>5.4</td>
<td>0.76</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.4 ± 5.8</td>
<td>27.1 ± 5.3</td>
<td>0.58</td>
</tr>
<tr>
<td>Resting heart rate, bpm</td>
<td>79 ± 12</td>
<td>81 ± 14</td>
<td>0.085</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>45</td>
<td>59</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>129 ± 25</td>
<td>138 ± 21</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>82 ± 11</td>
<td>82 ± 11</td>
<td>0.37</td>
</tr>
<tr>
<td>Current smoking history, %</td>
<td>15.1</td>
<td>20.3</td>
<td>0.052</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>4.8</td>
<td>8.8</td>
<td>0.013</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.61 ± 1.07</td>
<td>5.68 ± 1.12</td>
<td>0.44</td>
</tr>
<tr>
<td>HDL, mmol/L</td>
<td>1.34 ± 0.38</td>
<td>1.31 ± 0.40</td>
<td>0.24</td>
</tr>
<tr>
<td>ST depression ≥1 mm, %</td>
<td>6.1</td>
<td>6.1</td>
<td>0.99</td>
</tr>
<tr>
<td>FRS, points</td>
<td>6 ± 6</td>
<td>9 ± 5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean exercise capacity, MET</td>
<td>8.0 ± 2.7</td>
<td>6.2 ± 2.5</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Definitions are as in Table 1.

Exercise Test Results

The mean exercise capacity achieved was 8.0 ± 2.7 MET. The distribution of the exercise capacity achieved in this cohort was normally distributed and ranged from 1.5 to 20.0 MET (Figure 1B). The mean exercise capacity achieved by those who died was significantly lower than that of the survivors (6.2 ± 2.5 MET versus 8.0 ± 2.7 MET, P < 0.0001) (Table 2). Only 22% of those who died achieved the highest exercise capacity category (>8 MET) compared with 50% of those who survived (P < 0.001); 6.1% of the cohort had significant ST-segment depression (≥1 mm), and the presence of ST-segment depression did not differ between those who survived and those who died (Table 2).

Predictors of Death

The FRS and exercise capacity achieved with stress testing are independent predictors of death, when included in the same model (Table 3). This analysis was not adjusted for age, because the FRS includes age and the correlation between age and the FRS was very high (r = 0.74). There was no significant interaction between exercise capacity and the FRS (data not shown).

For every increase in exercise capacity by 1 MET, the risk of death was reduced by 17% (P < 0.001). Similarly, for every unit increase in the FRS, the risk of death increased by 9% (P < 0.001). Because a lower exercise capacity may reflect subclinical disease, an analysis was performed in which women with early deaths (deaths before the 5th year) were excluded (not shown). The association between exercise capacity, the FRS, and death remained the same.

The survival curves for this cohort by exercise capacity categories, after adjusting for the FRS, are shown in Figure 2B. When compared with the >8 MET group, there were significant differences in the mortality rate among the categories, in which the hazards ratio of death (with 95% CI) was 1.9 (1.3 to 2.9) for the 5- to 8-MET group (P = 0.002) and 3.1
A Kaplan-Meier survival curves for FRS tertiles. FRS tertiles are measured in points and categorized into tertile 1 (FRS 3), tertile 2 (FRS 4 to 9), and tertile 3 (FRS 10). The survival rate significantly decreased for each advancing FRS tertile (P<0.001) when compared with tertile 1 (least cardiac risk factors). B Kaplan-Meier survival curves for exercise capacity achieved on stress test at baseline, adjusted for FRS. Exercise capacity measured in units of MET and categorized as <5, 5 to 8, and >8 MET. Stratification between MET categories was based on the fact that the groups had distinctly different mortality rates (P<0.002) after adjusting for FRS.

Table 3. Hazards Ratio of Death of Independent Predictors of Mortality

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise capacity (for each 1-MET increment)</td>
<td>0.83</td>
<td>0.78–0.89</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FRS (for each unit increment)</td>
<td>1.09</td>
<td>1.05–1.13</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Discussion

We have shown that exercise capacity is a strong independent predictor of all-cause death in asymptomatic women, after adjusting for traditional cardiac risk factors. For each unit (1 MET) increase in exercise capacity, there was a 17% reduction in mortality rate.

Our data confirm the protective role of higher exercise capacity, even in the presence of established cardiac risk factors. Within this cohort of asymptomatic women, the risk of death doubled for those in the 5- to 8-MET exercise capacity category and tripled for those in the lowest (<5 MET) category when compared with the highest exercise capacity category and adjusted for the FRS.

The FRS and the Framingham Point Score (used in the Adult Treatment Panel III [ATP III] Report) are models used to predict the risk of cardiac disease in women. Both use a point system based on the presence or absence of cardiac risk factors to predict future cardiac events. These models, developed from the Framingham Heart Study and the Framingham Offspring Study, sum points for age, blood pressure, smoking status, total cholesterol (or LDL), and HDL. The difference between them is that the FRS incorporates diabetes into its score, whereas the ATP III guidelines state that the presence of diabetes is a cardiovascular disease equivalent. These prediction models are useful primary prevention devices that can estimate a person’s likelihood of future cardiac events, but neither model includes physical fitness (or lack thereof) as a cardiac risk factor within their model.

Our findings confirm that physical fitness, as measured by exercise capacity, is an independent risk factor for death in addition to other cardiac risk factors in asymptomatic women. Previous studies that have described this relation either did not include women or lacked the power to draw independent conclusions about women. Myers et al prospectively examined >6000 symptomatic men for a mean of 6.2 years. They found that for each 1-MET increase in exercise capacity, there was a 12% reduction in all-cause mortality rate. This study demonstrated the importance of physical fitness for symptomatic men, but our data show that exercise capacity is even more predictive in asymptomatic women.

Epidemiologic studies have noted that exercise capacity is an independent predictor of cardiovascular events and all-cause death in men. The Lipid Research Clinics Trial
and the Aerobics Center Longitudinal Study\textsuperscript{7,10} were able to demonstrate the association between physical fitness and death in asymptomatic men. Exercise scores that have been found to predict future cardiac events and death have included the duration of exercise (as a marker of exercise capacity) in the score, including the widely used Duke Treadmill Score.\textsuperscript{24,28–30}

The only study before the St James WTH Project that included asymptomatic women comes from the Cooper Clinic.\textsuperscript{15} Stress testing was performed on persons presenting for a preventive medical examination, including 3120 women. They found a trend of increased survival for women achieving higher exercise capacity levels, but only the lowest fitness quintile was significantly different from the highest four quintiles combined, after adjusting for cardiac risk factors. In contrast to our study, this study excluded those with diabetes, hypertension, an abnormal ECG (either at rest or with exercise), or inability to achieve 85% age-predicted heart rate. The restrictive exclusion criteria limit the generalizability of their findings. The St James WTH Project only excluded women who had a history of heart disease; target heart rate was not an end point of our stress testing. Our analysis confirms the trend seen in that study and is the first to demonstrate the association between exercise capacity and death in asymptomatic women.

There is significant evidence showing that decreased physical activity is associated with cardiac events and death in both men and women.\textsuperscript{25,27,31,32} Unlike physical fitness, which can be objectively measured, physical activity is a behavior, and how well it correlates with exercise capacity has not been extensively validated.\textsuperscript{16,33–36} Two studies that focused on women were based on the Framingham Heart Study\textsuperscript{32} and the Women’s Health Initiative (WHI) Observational Study.\textsuperscript{31} The Framingham Heart Study demonstrated a relation between physical activity and all-cause death. The WHI Observational Study was able to show an association between physical activity and cardiac events but concluded that women who engaged in both walking and vigorous activity for at least 2.5 hours per week carried a similar risk reduction of cardiac events when compared with less active women. In both studies, physical activity was assessed by a questionnaire and was essentially an estimate of activity status. Maximal exercise testing is an objective measure of physical fitness and is more readily quantifiable than assessment of physical activity.\textsuperscript{16,34}

There are limitations to our study. The voluntary nature of the cohort and the method by which women were recruited affected the demographic makeup of the cohort. Although the participants do not represent a random sample of women from the greater Chicago metropolitan area, estimates of the direction and strength of associations between the physiological variables of interest in this study should be valid for similar, community-dwelling populations of adult women in the United States seen in primary care settings, the population of interest. Also, exercise capacity was measured by using the speed and grade of the treadmill rather than by directly measuring the oxygen consumption, which is more accurate.\textsuperscript{35} Finally, our regression analyses demonstrate an association between exercise capacity and all-cause death, not causation. Nonetheless, it is clear that exercise capacity is a marker for risk of death.

The implications of our findings for clinical practice and health care policy are far reaching. The AHA and other such organizations want to find a noninvasive screening test that can predict cardiac risk in asymptomatic individuals to target primary prevention efforts.\textsuperscript{38,39} Currently, the ACC/AHA and other experts do not recommend using the standard exercise test for screening in asymptomatic individuals.\textsuperscript{3,40} However, our study has demonstrated the added value of stress testing asymptomatic women to assess a woman’s risk of death, in addition to traditional cardiac risk factors. We have demonstrated a clear clinical rationale for routine stress testing in asymptomatic women. Furthermore, the achieved exercise capacity should be interpreted and translated to the patient to provide important prognostic information.

Although our study did not test the hypothesis that improved physical fitness through training might improve prognosis, it is interesting to speculate that it might. A prospective study of 9777 asymptomatic men given a stress test at baseline and 5 years after found that individuals who either maintained or improved their exercise capacity had significantly lower all-cause and cardiovascular mortality rates than the “persistently unfit” men. Importantly, this study demonstrated a 7.9% decrease in all-cause mortality rate in men for an increase in treadmill time of $\approx$ 1 MET.\textsuperscript{10} In myocardial infarction survivors followed for 19 years, an increased exercise capacity of 1 MET was associated with an 8% to 14% reduction in mortality rate.\textsuperscript{41} High levels of physical fitness, as reflected by the exercise capacity achieved on a maximal stress test, have been shown to be protective of all-cause death in asymptomatic women.

Whether exercise capacity can be easily translated into a level of physical activity is still unknown and is an area in need of further research. Currently, the Surgeon General,\textsuperscript{42} the American College of Sports Medicine, the Centers for Disease Control and Prevention,\textsuperscript{43} and the AHA\textsuperscript{44} recommend that everyone should engage in a physically active lifestyle and that adults should perform moderately intense physical activity for at least 30 minutes per day, preferably every day. In the absence of specific data about the relation between physical activity and exercise capacity, continuing to encourage current physical activity recommendations seems appropriate.

The St James WTH Project confirms that exercise capacity is an independent predictor of death in asymptomatic women, even greater than that previously established among men.\textsuperscript{5,10} We were able to show a 17% reduction in mortality rate for every 1-MET increase in exercise capacity. Our findings strongly suggest that in addition to targeting traditional cardiac risk factors as part of the primary prevention evaluation, we must also evaluate the exercise capacity achieved on a maximal stress to fully assess a woman’s prognosis.

Acknowledgments

This study was supported by grants from AstraZeneca, DuPont Pharmaceuticals, the Irwin Foundation, Merck, Pfizer/Pharmacia, Siemens-Gammasonics, and St James Hospital. We acknowledge Dr Arfan Al-Hani, who designed the St James WTH Project. Without his foresight, enthusiasm, and dedication, this study would not exist.
His death is a loss to the investigators and participants of this study, as well as to the medical community at large. We are also indebted to the participants of the St James WTH Project, whose continued contribution to the study of heart disease in women is immeasurable.

References

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Circulation. 2003;108:1554-1559; originally published online September 15, 2003; doi: 10.1161/01.CIR.0000091080.57509.E9
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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