Prognostic Value of Treadmill Exercise Testing
A Population-Based Study in Olmsted County, Minnesota

Veronique L. Roger, MD, MPH; Steven J. Jacobsen, MD, PhD; Patricia A. Pellikka, MD; Todd D. Miller, MD; Kent R. Bailey, PhD; Bernard J. Gersh, MB, ChB, DPhil

Background—The prognostic value of treadmill exercise testing (TMET) has been studied in selected populations. The generalizability of these data to different populations and to women is uncertain.

Methods and Results—A retrospective, population-based cohort study of all persons (1452 men and 741 women) who underwent TMET in years 1987 to 1989 in Olmsted County, Minnesota, was undertaken. Individuals were followed up for all-cause mortality and cardiac events (cardiac deaths, nonfatal myocardial infarction, or congestive heart failure). Sex-specific analyses were performed to determine whether the predictors of outcome and the magnitude of the associations were similar in both sexes. In men, 77 deaths and 106 cardiac events occurred during 8956 person-years of observation; in women, 46 deaths and 54 cardiac events occurred during 4801 person-years of follow-up. Exercise-induced angina, ECG changes, and workload achieved on the TMET were strongly associated with all-cause mortality and cardiac events in both sexes, and the strength of the association was similar. After adjustment, workload was the only TMET variable associated with outcome. A higher workload was associated with a reduction in the risk of cardiac events and of all-cause mortality; the protective effect of exercise capacity was strong and was similar in both sexes.

Conclusions—In this population-based cohort, exercise capacity was the TMET variable that exhibited the strongest association with all-cause mortality and cardiac events. This protective effect of exercise capacity was observed in both sexes. (Circulation. 1998;98:2836-2841.)

Key Words: exercise ■ women ■ epidemiology

Treadmill exercise testing (TMET) is used widely in the United States, and its use is associated with the use of “downstream” cardiac procedures.1 However, its overall value with regard to risk stratification is not fully characterized.

Studies that examined the prognostic value of TMET have been conducted on selected populations. Thus, the generalizability of these results is uncertain. Furthermore, studies have not been entirely consistent with regard to the identification of the prognostic factors that can be derived from TMET.2,3 These differences may be the result of the use of different populations. Some studies4–8 included patients from referral centers with cardiac symptoms or who had undergone angiography. Conversely, other studies3 were conducted in preventive medicine clinics among apparently healthy individuals who may have healthier life habits that are associated with better outcomes compared with the general population.

The selected nature of the study populations leads to the underrepresentation of certain groups. For women, it is well recognized that the diagnostic yield of TMET is lower than for men,2 but there is little information on its prognostic value. Indeed, some prognostic studies of TMET included predominantly5,6,8,10 or exclusively11 men. In addition, most studies that included women did not report sex-specific analyses5,6,8,10 thereby precluding the testing of sex differences in the prognostic value of TMET. Studies that included sex-specific analyses reported inconsistent results on the prognostic value of TMET in women.3,4

The results of these studies leave uncertainties with regard to their external validity. This calls for additional data to address this issue in more-representative samples derived from a geographically defined population and, in particular, to answer the question of the appropriateness of the use of TMET for risk stratification in women. Recent exercise testing guidelines2 acknowledge such a gap in knowledge. The purpose of the present study was to examine the outcome after TMET in a geographically defined population to characterize the TMET variables associated with outcome and to test whether this association is similar in both sexes.

Methods

Study Setting

The population of Olmsted County, Minnesota, is served by a largely unified medical care system that has accumulated comprehensive clinical records over an extended period, and nearly all medical care
is delivered to local residents by a few providers, mainly the Mayo Clinic and the Olmsted Medical Group. Approximately 70% of the Olmsted County population (1990 census: 106 470) resides in Rochester. In 1990, the population was 96% white, and 82% of the adult population had graduated from high school. With the exception of a higher proportion of the working population employed in the healthcare industry, the demographic characteristics of the population of Olmsted County are similar to those of other US whites.

The epidemiological potential of this situation is enhanced by the fact that each provider uses a record system, which assembles in one place the details of every hospitalization, outpatient visit, and laboratory reports. These records are easily retrievable because since the early 1960s, the Mayo Clinic has maintained extensive indexes based on clinical and histological diagnoses and surgical procedures. The Rochester Epidemiology Project has developed a similar index for the records of other care providers, resulting in the linkage of medical records from essentially all sources of medical care used by the Olmsted County population.

Study Population
A retrospective, population-based cohort of Olmsted County residents who underwent TMET between January 1, 1987, and December 31, 1989, was identified. Residency in Olmsted County was verified by information from the medical record and city and county directories. Analysis included all persons who underwent initial TMET. The medical record was reviewed by trained nurse abstractors to collect demographics and clinical information. Comorbid conditions were recorded with the use of the Charlson index, which is a validated weighted index that combines the number and seriousness of comorbid conditions.

Exercise Tests
The indications for TMET were as follows:

1. Evaluation of documented coronary artery disease (CAD), defined by the presence of any of the following criteria: prior myocardial infarction (MI) or revascularization procedure (CABG or PTCA) or significant coronary disease at angiography.
2. Diagnostic, if the patient had dyspnea or chest pain but no documented CAD.
3. Other, in the absence of symptoms or documented CAD. These included risk stratification before noncardiac surgery or evaluation of sedentary persons before they began an exercise program.

All tests were ordered by physicians and performed with standard protocols (Bruce, modified Bruce, or Naughton). The decision to interrupt medications before TMET was at the discretion of the attending physician. The estimated workload was expressed in metabolic equivalents (METs). The value for METs was estimated from standard published tables based on protocol and duration of exercise.

The positivity of the exercise ECG was determined by conventional criteria (≥ 1 mm of horizontal or downsloping ST-segment depression at 80 ms after the end of the QRS complex [from the J point]). The results of the exercise ECG were classified as negative, positive, markedly positive (if ST-segment depression exceeded 2 mm), or nondiagnostic.

Ascertainment of End Points
The end points of interest, which were ascertained from the medical records, were death and cardiac events, defined as cardiac death, nonfatal MI, or congestive heart failure. The State of Minnesota death certificate files, to which the records of all Olmsted County residents are linked, were used to classify deaths as cardiac, cancer, and other. For MI, a clinical definition was used that incorporated the occurrence of chest pain typical for an ischemic origin and characteristic changes in the ECG and cardiac enzymes. For congestive heart failure, a clinician’s diagnosis was used.

Reliability Evaluation
Reliability of the data collection was evaluated in a random sample of 20 cases. The κ-coefficient, which measures agreement beyond that expected by chance alone, was used to evaluate interobserver and intraobserver variability. By convention, arbitrary categories of κ were used to define poor (κ≤0.4), fair to good (0.4<κ≤0.7) and excellent (κ>0.7) agreement beyond chance. The variables included comorbid conditions, symptoms, test results, occurrence of MI, congestive heart failure, and cause of death.

Statistical Analysis
Comparisons of baseline characteristics between men and women were made with χ² tests for categorical data and t tests for continuous variables. Survival was estimated by the Kaplan-Meier method. Cox proportional hazard models were constructed to determine the association of predictor variables with all-cause mortality and cardiac events. The variables included in the models were age, presence of symptoms, history of MI, coronary disease risk factors (hypertension, diabetes mellitus, smoking, hyperlipidemia, and familial coronary disease), obesity (by use of body mass index), Charlson index, angina on the TMET, positive exercise ECG, and workload achieved (in METs). Workload achieved (in METs) was modeled as a continuous variable; to detect a nonlinear component to the relationship, quadratic models were also fitted. Separate models were constructed for men and women. A combined model was used to test for interaction between sex and other variables. To diminish the influence of subclinical disease on the observed results, analyses were repeated after early deaths, ie, persons who died during the first 3 years of follow-up, were excluded.

Results
During the study period, 2193 initial TMETs were performed in 741 women and 1452 men in Olmsted County, Minnesota. Sixteen percent of these individuals (191 men and 152 women) were ≥65 years of age.

Baseline Characteristics
Women were older, more likely to be symptomatic, and more likely to be taking antianginal medications (Table 1). They were more likely to be hypertensive and hyperlipidemic. Women had a higher Charlson index. This was not accounted for by the age difference, because age stratification did not modify this sex difference in the Charlson index.

Indications and Results of the Stress Test
More women than men underwent TMET for diagnostic purposes (Table 2). The majority (86%) of the persons exercised according to a Bruce protocol, whereas Naughton or modified Bruce protocols were used for the remainder (14%). Men exercised to a higher workload (Figure). There were similar percentages of positive TMET in both sexes.

Outcome
The mean follow-up was 6.3±2.0 years. In men, 77 deaths and 106 cardiac events (17 cardiac deaths, 60 nonfatal MIs, and 29 cases of congestive heart failure) occurred during 8956 person-years of observation. In women, 46 deaths and 54 cardiac events (9 cardiac deaths, 28 nonfatal MIs, and 17 cases of congestive heart failure) occurred during 4801 person-years of follow-up (Table 3). The event-free survival rate was 96% at 5 years for all-cause mortality and 93% for cardiac events for both men and women.
TABLE 2. Indications and Test Results in both sexes.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Men (n=1452)</th>
<th>Women (n=741)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indications, %</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diagnostic</td>
<td>41</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>Evaluation of documented CAD</td>
<td>9</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>51</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Results</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Workload, METs</td>
<td>10.9±3.5</td>
<td>8.5±3.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peak rate-pressure product</td>
<td>29395±6750</td>
<td>26173±5873</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Exercise test positive, %</td>
<td>8</td>
<td>8</td>
<td>0.99</td>
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</tbody>
</table>

All-Cause Death

Associations between clinical and TMET variables and time to death are shown in Table 4. The achieved workload exhibited the strongest univariate association with time to death; once it was entered in the model, neither the result of the exercise ECG nor exercise-induced angina was associated with mortality.

Adjustment for age and comorbidity did not alter the association between workload and time to death (Table 4). The direction of the association indicated a protective effect. An increase in 1 MET in the workload was associated with a 20% risk reduction in men and a 25% risk reduction in women. This difference was not significant. There was no interaction between sex and any of the variables tested.

Because a lower exercise capacity may reflect subclinical disease, analyses were conducted after early deaths were excluded. The association between workload achieved and death remained strong, consistent, and statistically significant in both sexes.

Cardiac Events

Associations between clinical and TMET variables and cardiac events are shown in Table 5. There were interactions between sex and several clinical variables, including age (P=0.03), Charlson index (P=0.09), prior MI (P=0.01), symptoms (P=0.05), and workload (P=0.004). This indicated that sex was an effect modifier of the association between each of these variables and cardiac events.

All 3 TMET variables were univariately associated with the risk of cardiac events. Age, coronary disease risk factors, and the Charlson index were potential confounders of the association between workload and cardiac events. After adjustment for these variables, the protective association between workload and cardiac events remained significant. An increase of 1 MET in the workload was associated with a 17% decrease in risk in men and a 23% decrease in women.

Once these variables were entered in the model, addition of the other 2 TMET variables did not improve the fit of the model and did not confound the association between workload and outcome. Neither positive exercise ECG nor exercise-induced angina was independently related to time to cardiac event after workload was taken into account. The results were unchanged when the analyses were repeated with cardiac death as the end point or with cardiac events defined as cardiac death or nonfatal MI as the end point.

Stratified analysis showed a protective effect of workload in both symptomatic and asymptomatic men and women and for both death and cardiac events. The addition of a quadratic term for METs did not improve the fit of the model, which suggests no evidence of a nonlinear component to the relationship.

Analysis of interobserver variability showed excellent agreement (κ>0.7) for all but 4 (chronic obstructive lung disease, hyperlipidemia, familial coronary disease, and type of chest pain) of the 23 test variables. These variables were reabstracted.

Discussion

In this geographically defined population, we observed a strong association between the results of TMET and outcome. Exercise capacity, exercise-induced angina, and a positive exercise ECG were univariately associated with outcome. In multivariate analysis, workload was the only TMET variable significantly predictive of outcome. There was a strong linear relationship between increasing workload and outcome, with an increment of 1 MET in the workload achieved being associated with a 20% to 25% reduction in the risk of death and cardiac events. Exclusion of early deaths did not alter this association, which suggests that it is not explained by subclinical disease, which strengthens causality. The protective effect of exercise capacity was similar in men and women.

TMET Variables and Outcome

Several studies have examined the association between TMET variables and outcome. Some earlier studies were conducted without multivariate analysis, and thus the independent contribution of each variable to outcome could not be determined. The Exercise Unit of Seattle Heart
Watch17,18 provided important data on the prognostic value of TMETs in a population of healthy volunteers and emphasized the importance of exercise capacity. However, as acknowledged by the authors,17 the number of women was small and did not allow the sex-specific analyses necessary to establish the prognostic value of TMETs in women. In addition, the study population consisted of volunteers and was subject to the healthy-participant effect, which compromises external validity.19 Similar limitations apply to the Baltimore Longitudinal Study of Aging.20

Important studies from Duke University Medical Center have led to the development of a TMET score based on hospitalized patients that incorporates exercise duration, magnitude of ST-segment deviation, and exercise-induced angina.5 This score was subsequently validated in the outpatient setting, leading to the recommendation of the use of the Duke score as part of TMET.2 Although exercise duration was clearly an independent predictor of outcome in the Duke inpatient study, it exhibited a weaker association with outcome than the other components of the score. In the outpatient setting, however, the respective prognostic value of each of the 3 components of the score was not individually examined.9 The Duke inpatient series had substantially different characteristics than the present population-based cohort.5,9 In particular, patients in the study had more symptoms and a higher frequency of coronary disease. Statistical adjustment through multivariate modeling controls for such measurable characteristics but cannot eliminate residual confounding such as can be caused by unmeasured differences between 2 populations. These differences likely play a role in the differences in the respective prognostic value of the workload and of the ECG results between the Duke population and the present cohort. This underscores the importance of examining the characteristics of the populations in which such indicators may be used. However, the protective effect of workload observed in our series remained unchanged with stratification according to symptom status. The fact that other variables such as exercise-induced angina or ST-segment depression were not independent predictors of outcome once clinical variables and workload were taken into account in the present study is likely related to the association between clinical and TMET variables. The Duke outpatient study differs from the present study with regard to the selection of clinical prognostic indicators.9 A recent report from CASS4 also underscored the prognostic value of exercise capacity. It differed from the present study in that exercise-induced ST-segment depression was not associated with outcome in the Olmsted County population. These differences between the CASS report and the present data are likely related to differences in the 2 populations, because CASS patients had undergone coronary angiography, and the majority had a history of MI.

Exercise Capacity and Outcome

Overall Effect

In the present cohort, the protective effect of exercise capacity was apparent for both cardiac events and all-cause mortality. To the best of our knowledge, the association between exercise capacity as objectively measured with TMET and outcome has not been reported in a population-based setting. Previous reports were derived from selected groups of persons self-referred to a preventive medicine facility, and therefore, their external validity may be questioned.3 The results of the present study, derived from a geographically defined cohort of individuals referred by physicians, support the generalization of the conclusions of prior studies and serve to minimize the concern for confounding by association with other healthy behaviors in selected individuals.

Effect in Women

Previous studies that have underscored the beneficial effect of physical activity on outcome involved primarily or exclu-

**TABLE 3. Distribution of Events by Sex**

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
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<tbody>
<tr>
<td>Deaths</td>
<td>77</td>
<td>46</td>
</tr>
<tr>
<td>Cardiac, n (%)</td>
<td>25 (32)</td>
<td>16 (35)</td>
</tr>
<tr>
<td>Cancer, n (%)</td>
<td>27 (35)</td>
<td>13 (28)</td>
</tr>
<tr>
<td>Other causes, n (%)</td>
<td>25 (32)</td>
<td>17 (37)</td>
</tr>
<tr>
<td>Cardiac events</td>
<td>106</td>
<td>54</td>
</tr>
<tr>
<td>MI, n (%)</td>
<td>60 (57)</td>
<td>28 (52)</td>
</tr>
<tr>
<td>Congestive heart failure, n (%)</td>
<td>29 (27)</td>
<td>17 (31)</td>
</tr>
<tr>
<td>Cardiac deaths, n (%)</td>
<td>17 (16)</td>
<td>9 (17)</td>
</tr>
</tbody>
</table>

% denotes percent of all events attributable to a given category.
sively men. In studies that included women, the evidence for a protective effect of physical activity was less strong and less consistent than in men. Methodological differences in the measurement of physical activity may explain this variance.

Recently, important data have been reported from a large cohort of women that show a protective effect of physical activity as measured by self-report. Because that cohort included only women, it cannot examine sex differences in the association between physical activity and outcome. In addition, these data are not exempt from biases, including nonrandom misclassification as a result of overreporting of physical activity. Furthermore, external validity remains a concern for any such cohort study because of voluntary participation.

Study Limitations
External validity is a challenge for studies of exercise testing. Indeed, the recruitment of volunteers exposes the cohort to the healthy-volunteer effect, whereas the selection of heart disease patients provides a cohort of “sicker” individuals, yielding results equally difficult to extrapolate to the general population. One could propose that the present series, which reports on the comprehensive experience of community-dwelling adults, may have enhanced external validity compared with some previously published work. However, because the population of Olmsted County is overwhelmingly white (98%), it is uncertain whether

<table>
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<th>TABLE 4. Predictors of Time to Death</th>
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<tbody>
<tr>
<td><strong>Women</strong></td>
</tr>
<tr>
<td><strong>RR (95% CI)</strong></td>
</tr>
<tr>
<td><strong>Univariate analysis</strong></td>
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<tr>
<td>Age</td>
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<tr>
<td>Charlson index</td>
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<tr>
<td>Prior MI</td>
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<tr>
<td>Symptoms*</td>
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<td>Risk factors†</td>
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<tr>
<td>Angina with TMET</td>
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<tr>
<td>Positive ECG</td>
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<tr>
<td>Workload</td>
</tr>
<tr>
<td><strong>Multivariate analysis</strong></td>
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<tr>
<td>Age</td>
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<tr>
<td>Charlson index</td>
</tr>
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<td>Workload</td>
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*Absence of symptom is the reference level. †Absence of risk factor is the reference level.

<table>
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<th>TABLE 5. Predictors of Time to Cardiac Event</th>
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<tr>
<td><strong>Women</strong></td>
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<tr>
<td><strong>RR (95% CI)</strong></td>
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<td><strong>Multivariate analysis</strong></td>
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<tr>
<td>Charlson index</td>
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<tr>
<td>Age</td>
</tr>
<tr>
<td>Numbers of risk factors</td>
</tr>
<tr>
<td>Workload</td>
</tr>
</tbody>
</table>

*Absence of symptom is the reference level. †Absence of risk factor is the reference level.
these data would apply to different populations, thus underscor-
ing the need for additional studies.

As indicated by the frequency of asymptomatic persons in this
cohort, a relatively large proportion of indications for testing
could be categorized as class IIb of the “Guidelines for Exercise Testing” in effect at that time.24 However, the data reported
herein represent the comprehensive experience of the Olmsted
County population during this time period, and the analysis of
practice patterns is beyond the scope of this study.

Conclusions
The present study demonstrates, in a geographically defined
population, a strong protective association between exercise
capacity and outcome. The protective effect of exercise
capacity is similar in men and women.

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Association National Center (93-1325 and 96-1358) and a grant from the
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