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Gender Differences in the Prognostic Value of Exercise Treadmill Test Characteristics

Stacie L. Daugherty, MD, MSPH[*,†], **David J. Magid, MD, MPH**[*,†], **Jennifer R. Kikla, MSPH**[‡], **John E. Hokanson, PhD**[*], **Judith Baxter, MA**[*], **Colleen A. Ross, MS**[†], and **Frederick A. Masoudi, MD, MSPH**[*,†,§] **on behalf of the Colorado Cardiovascular Outcomes Research Group**

[*] University of Colorado Denver, Aurora, Colorado

[†] Institute for Health Research, Kaiser Permanente of Colorado, Denver, Colorado

[‡] Longmont United Hospital, Longmont CO

[§] Denver Health Medical Center, Denver, Colorado

Abstract

Background—Although exercise treadmill testing (ETT) is known to be less sensitive and specific for diagnosis of coronary disease in women, little is known about gender differences in the prognostic importance of ETT variables.

Methods—We studied9569 consecutive patients (46.8% women) referred for ETT between July 2001- June 2004 in a community-based system. We assessed the association between ETT variables (exercise capacity, symptoms, ST-segment deviations, heart rate recovery, and chronotropic response) and time to all-cause death and myocardial infarction adjusting for patient and stress test characteristics. Models were stratified by gender to determine the relationship between ETT variables and outcomes.

Results—In the entire population, exercise capacity and heart rate recovery were significantly associated with all-cause death, whereas, exercise capacity, chest pain and ST-segment deviations were significantly associated with subsequent MI. The relationship between ETT variables and outcomes were similar between men and women except for abnormal exercise capacity, which was had a significantly stronger association with death in men (men: HR = 2.89, 95% CI 1.89–4.44; women: HR = 0.99, 95% CI 0.52–1.93; interaction <p=0.01); and chronotropic incompetence, which had a significantly stronger relationship with MI in women (men: HR = 1.29, 95% CI 0.74–2.20; women: HR= 2.79, 95% CI 0.94–8.27; interaction p =0.04).

Conclusions—While many traditional ETT variables had similar prognostic value in both men and women, exercise capacity was more prognostically important in men and chronotropic incompetence was more important in women. Future studies should confirm these findings in additional populations.

Corresponding Author: Stacie L. Daugherty, MD, MSPH, University of Colorado Denver, Division of Cardiology, 12631 E. 17 th Avenue, B130, PO Box 6511, Aurora, CO 80045, Phone: 303-724-2089, Fax: 303-724-2094, stacie.daugherty@ucdenver.edu.

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Keywords

gender differences; stress testing; prognosis

Background

The exercise treadmill test (ETT) is a diagnostic and prognostic tool used to identify patients at risk for coronary artery disease, cardiac events and death. While in the past, the interpretation of the ETT primarily focused upon ST-segment changes on the electrocardiogram (ECG), exercise capacity, and symptoms occurring during exercise, a range of other variables including heart rate recovery and chronotropic incompetence have emerged as important prognostic factors.[1–7] Some studies suggest that these variables carry more predictive value compared to traditional variables, including the Duke treadmill score (DTS), which is a composite of ST-segment deviation, exercise time and exercise-induced angina.[6, 8–12]

Gender based differences in the value of ETT for the purposes of establishing the diagnosis of coronary artery disease have been documented; it is recognized that for women, the diagnostic specificity of the ST segment depression during ETT is lower than it is for men.[13, 14] However, gender differences in the prognostic importance of other ETT variables, outside of ST segment changes alone, have not been well characterized. Moreover the few studies that have assessed whether additional ETT variables are equally prognostic in men and women, have been inconclusive.[10, 11, 15]

The primary objective of the present study was to investigate gender differences in the association between a wide range of ETT variables and outcomes. Specifically, this report examined five ETT variables (exercise capacity, significant ST-segment deviations during test, chest pain during test, heart rate recovery, and chronotropic incompetence) and their relationship with future myocardial infarction (MI) and all-cause mortality by patient gender in a population of men and women undergoing routine ETT at a large integrated healthcare system. The results are intended to determine whether risk markers identified during ETT should be considered separately depending upon the gender of the patient tested.

METHODS

The study population was derived from a clinical registry of consecutive Kaiser Permanente of Colorado (KPCO) members aged 18 years and older referred for ETT between July 2001 and June 2004. KPCO is an integrated, nonprofit managed care organization that provides medical services to more than 460,000 members in the Denver, Colorado metropolitan area. The KPCO membership is demographically similar to the insured population of the Denver metropolitan area and includes patients covered by Medicare and Medicaid.

Clinical and Exercise Data

Prior to the ETT, the clinician conducting the test performed a structured history and medical record review to document symptoms, medication use, cardiac risk factors, prior cardiac events and procedures. Additional data regarding coexisting illnesses (e.g., cerebrovascular and peripheral vascular disease) were obtained from KPCO administrative databases. For patients undergoing multiple tests during this period, only data from the first was included. All patients underwent a symptom limited ETT according to standardized protocols with exercise and recovery data recorded; the majority of patients (~85%) were tested with the standard Bruce protocol.[14] During each stage of exercise and recovery, symptoms (e.g., chest pain, shortness of breath, fatigue), blood pressure, heart rate, cardiac

rhythm, and workload were entered contemporaneously into the computerized registry which was linked to administrative and clinical databases to obtain information on subsequent hospitalizations and vital status. Tests were supervised by physicians certified in ETT interpretation.

Independent Variables

Based on prior literature, the primary variables assessed for prediction of outcomes included chest pain during the test, exercise capacity, heart rate recovery, significant ST-segment deviations during the test, and chronotropic incompetence.[1–7] Chest pain was considered present if the examining provider recorded that the patient developed either limiting or non-limiting chest pain during the study. Exercise capacity was recorded in metabolic equivalents (METs). In addition, age and gender adjusted peak workload achieved, or proportional METS, was determined; a value less than 85% of predicted peak workload for age and gender was considered abnormal.[12, 16] Heart rate recovery (HRR) was defined as the decrease in heart rate between peak exercise and at one minute in recovery. For analytic purposes, a cutoff value of 12 beats/minute or less was considered an abnormal HRR.[6] Chronotropic incompetence was considered present if less than 80% of a patient's heart rate reserve (calculated as 220 –age – resting heart rate) was used at peak exercise.[3, 7] For patients on beta blockers a value less than 64% was considered abnormal.[17] Significant ST-segment deviations were considered present if there was at least 1.0 mm of horizontal or downsloping ST segment depression or any pathological ST-segment elevation recorded by the supervising physician.

Other variables collected at the time of ETT or from KPCO administrative data were considered as possible confounders. These variables included patient age; cardiac risk factors (family history of cardiac disease, smoking status, hypertension, diabetes mellitus, hyperlipidemia); coexisting illnesses (a history of coronary heart disease, a history of chronic obstructive pulmonary disease, peripheral vascular disease, cerebral vascular accident, obstructive sleep apnea, cancer, or depression); medication use (self- reported use of beta-blockers, calcium channel blockers, angiotensin converting enzyme inhibitors or angiotensin receptor blockers, statins, aspirin and diuretics at time of ETT); and additional ETT variables (maximal heart rate response, maximal BP response, and ventricular ectopy in recovery).

Outcome Variables

The primary outcomes for this study were 1) all-cause mortality and 2) hospitalization for myocardial infarction (MI) over a mean follow-up of 3.2 years after ETT. Data on all-cause mortality was validated through a comparison with internal KPCO data sources and the State of Colorado death certificates. Deaths were verified by a panel of the investigators blinded to the clinical and exercise data. All hospitalizations for KPCO members were included in the administrative data and identified by primary diagnostic codes. MI hospitalizations were based on a principal inpatient ICD-9 diagnosis code of 410.×. Importantly, data on hospitalizations occurring outside of KPCO were available through administrative claims data, which are considered highly accurate as they are used for reimbursement for out-of-system utilization.

Statistical Analyses

Baseline demographic factors, co-morbidities, exercise variables and outcomes were compared between men and women using the chi-square test for categorical variables and t-test for continuous variables.

Freedom from all-cause mortality and the occurrence of each outcome (death and non-fatal MI) were compared using the Kaplan-Meier method. Freedom from an event was measured from the time of the first ETT and censored at the time of the event of interest. Differences in event rates were evaluated with a log-rank test. Next, to assess the independent relationship between the five ETT predictor variables and outcomes, Cox proportional hazards models were constructed, adjusting for the patient-level variables listed in Table 1. For the outcome of MI, standard Cox models may provide biased estimates risk due to the competing risk of death. Therefore, we adjusted the MI risk estimates accounting for the competing risk of death.[18]

To obtain gender-specific estimates for the relationships between the ETT variables and outcomes, the Cox proportional hazards models were stratified by gender. The statistical significance of any gender-related differences in these relationships was ascertained using two-way interaction terms in the full multivariable models.

To assess the robustness of the results, a secondary analysis was performed. Models for both outcomes were constructed that included all 5 of the ETT predictor variables together to determine their association with the outcomes independent of the other ETT variables. Similar relationships were seen as in the primary analyses and these results are not reported.

The study was approved by the Kaiser Permanente Colorado Institutional Review Board. All analyses were performed using the SAS statistical package version 9.1 (SAS Institute, Cary, NC). This study was funded in part by CV Therapeutics, Inc. The sponsors were not directly involved in the design and conduct of the study, in the collection, management, analysis, and interpretation of the data, or in the preparation of the manuscript. Dr. Daugherty is supported by Award Number K08HL103776 from the National Heart, Lung and Blood Institute. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

RESULTS

Baseline Characteristics and Events

Of the 9569 patients undergoing ETT, 5094 (53%) were men, who were on average younger, and were more likely to have a history of coronary artery disease. The main reason for a referral for an ETT was atypical chest pain (men =46.8%, women = 47.9%; p=0.49). During the ETT, women were more likely to experience chest pain; had worse exercise capacity on average; higher rates of abnormal heart rate recovery; and higher rates of chronotropic incompetence compared with men. (Table 1)

During a mean follow-up of 3.2 years, there were a total of 142 deaths from any cause and 130 MIs. Men had a higher rate of death (1.9% vs. 1.1% among women, p=<0.01) and MI (2.0% vs. 0.6% among women, p<.01).

ETT Variables and Risk of All-cause Mortality

Associations between the 5 ETT variables and time to death are shown in Table 2. Among all patients, only exercise capacity and heart rate recovery were significant predictors of all-cause mortality. Exercise capacity had the strongest magnitude of association with death (HR 2.00, 95% CI 1.42–2.85) among all patients.

In the models stratified by patient gender, exercise capacity (HR 2.89, 95% CI 1.89–4.44 for peak workload <85% predicted) and heart rate recovery (HR 1.70, 95% CI 1.09–2.65) were significantly associated with all-cause mortality in men. In women, none of the exercise parameters tested was significantly associated with all-cause mortality (Table 2).

A significant interaction was identified between gender and exercise capacity with respect to all-cause mortality (men: HR 2.89, 95% CI 1.89–4.44; women: HR 0.99, 95% CI 0.52–1.93; p=<0.01 for interaction). No other significant gender interactions were found for all-cause mortality. (Table 2)

ETT Variables and Risk of Non-fatal MI

The associations between ETT variables and non-fatal MI accounting for the competing risks of death are shown in Table 3. After adjustment, exercise capacity, chest pain and significant ST-segment deviations were predictive of MI for all patients. The ETT variable associated with the greatest magnitude of risk for MI was exercise capacity (HR = 2.43, 95% CI 1.69–3.49).

In the gender-stratified models, significant predictors of MI for both men and women included exercise capacity, chest pain and significant ST segment deviations. Reduced exercise capacity was associated with the largest magnitude of risk for MI for men (HR 2.42, 95% CI 1.61–3.66) and chest pain during the test had the largest magnitude of risk for MI for women (HR 3.18, 95% CI 1.37–7.36). (Table 3)

The magnitude of the association between increased risk of MI and chronotropic incompetence and significant ST-segment deviations was greater in women compared to men (Table 3). The interaction between chronotropic incompetence and gender was statistically significant (p-value for the interaction= 0.04, Table 3), indicating that chronotropic incompetence was a stronger predictor of MI in women than for men.

DISCUSSION

Among this community-based cohort of patients undergoing ETT with long-term follow-up, we found significant associations between ETT variables and the outcomes of all-cause mortality and MI for men and women. However, the magnitude of some of these associations tended to vary by patient gender. Specifically, decreased exercise capacity was almost two times more highly associated with all-cause mortality in men compared to women (p-value for interaction <0.01). Although chronotropic incompetence was not independently associated with MI overall, the relationship between chronotropic incompetence and MI in women was significantly stronger than in men (p-value for interaction 0.04) and bordered on predictive significance for MI among women. Thus, for prognostic purposes, the interpretation of ETT results based upon traditional parameters may differ for men and women.

The findings of our study in the overall population are consistent with previous research identifying reduced exercise capacity, abnormal heart rate recovery, chest pain, and significant ST-segment deviations during ETT as independent predictors of mortality and cardiac events.[1–11] Similar to prior studies that have evaluated the prognostic associations of ETT variables, exercise capacity emerged as the variable with the strongest risk association for both outcomes in our study population.[8, 10, 15] However, this study importantly expands the literature by demonstrating the magnitudes of association between ETT variables and outcomes for men and women.

In particular, we found substantial differences between men and women with respect to the implications of exercise capacity on the risk of death. Men with decreased exercise capacity had a risk of death two times that of women with decreased exercise capacity. Although the findings should not be interpreted to indicate that exercise capacity is not of any prognostic importance in women due to the wide confidence intervals around the estimate of association, the interaction suggests that limited exercise capacity is of greater prognostic

importance in men than in women. Prior work among populations of asymptomatic women have shown that exercise capacity is predictive of all cause death in women.[9, 15] One of the few prior studies to investigate differences in the prognostic importance of exercise capacity in both genders found no significant interaction for the outcome of all-cause death.[19] However, the Olmsted County study had substantially different characteristics than the present study. In particular, patients in the study were younger, were more often asymptomatic at time of ETT and peak workload was calculated based on historical guidelines instead of more recent gender specific alogrithms.[10, 12] These differences likely play a role in the lack of gender specific prognostic differences in exercise capacity for death between the Olmsted county population and the present cohort. In contrast, the Olmsted county study did find a significant interaction between gender and the association between cardiac events which included cardiac death, non-fatal MI or congestive heart failure. The current study investigated all cause death and non-fatal MI individually and only found a significant gender difference in the prognostic value of exercise capacity for death ($p=<0.01$ for interaction). Future studies should further investigate the role of exercise capacity with prognosis in men and women.

Chronotropic incompetence also exhibited a differential relationship with the risk of MI by gender, with a greater prognostic importance in women than in men. We found a modest association between chronotropic incompetence and MI in men and a substantially stronger association between chronotropic incompetence and MI in women which bordered on statistical significance. (Table 3) To our knowledge, this is the first study that identifies potentially important gender-based differences in this relationship with MI.[3, 7, 17, 20] Previous studies that included women in their population did not present gender-specific findings. [3, 7, 21] Our results suggest that gender specific estimates of chronotropic incompetence may provide more nuanced prognostic information compared to the overall population effect.

In regards to the other ETT variables studied, we found no significant gender differences in the association of heart rate recovery, chest pain during the test or significant ST segment deviations with either outcome. Prior work has similarly found no significant gender difference in the association between heart rate recovery and all cause mortality.[2, 6, 22]

Given the independent importance of many ETT variables in predicting outcomes in men and women, a composite score may be the most useful prognostic tool. In fact, clinical guidelines for exercise testing suggest that exercise scores be used in the interpretation of exercise tests and in clinical decision-making.[14] Exercise test scores have been widely used to improve the predictive accuracy of the treadmill test and provide prognostic estimates of cardiac risk.[23, 24] However, most scores were developed from populations composed primarily of men and few scores have been designed specifically for women.[12, 25] Finally, most composite scores do not account for chronotropic incompetence; a variable that may provide different prognostic information based on gender. Our study further highlights the importance of understanding the variability in the impact of ETT variables and prognosis based upon gender, supporting the development of gender-specific risk estimates.

Certain factors should be considered in the interpretation of these results. First, the overall number of cardiac events and deaths was low in this population especially for women. Thus, this study has limited power to identify other potentially clinically important differences in the relationship between ETT variables and outcomes by gender. Further, the presence of clinically meaningful association of exercise test variables with cardiac events and death among women and men cannot necessarily be excluded when it was not present statistically. However, this study was drawn from a large population of unselected patients undergoing exercise testing with excellent record keeping and follow-up. In addition, it is possible that

unmeasured confounders could alter the relationships found. Finally, while these findings are applicable to this integrated healthcare system, the results may not apply to other healthcare systems. However, Kaiser Colorado cares for a large, diverse patient population that is generally representative of the insured Colorado population. Our findings should be validated in other populations.

Conclusion

The current study suggests that the prognostic importance of some exercise testing variables may differ based upon a patient's gender. Estimates based on overall population risks associated with exercise parameters may thus provide less useful estimates than those that acknowledge the variability in risk associated with patient gender. This study supports the need for future research in this area and the potential need for development of gender-specific calculations for better risk stratification following ETT.

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Table 1

Baseline characteristics of the study population referred for an ETT

Characteristic	Total n = 9569	Men n= 5094	Women n=4475	P-value
Age (years)	56 (48, 65)	55 (47, 65)	57 (49, 66)	<0.01
Current smoking	1348 (14.1)	729 (14.3)	619 (13.8)	0.52
Clinical History				
Diabetes Mellitus	1341 (14.1)	781 (15.3)	560 (12.5)	<0.01
Hypertension	4664 (48.7)	2463 (48.4)	2201 (49.2)	0.43
Hyperlipidemia	6083 (63.6)	3279 (64.4)	2804 (62.7)	0.09
Coronary artery disease	1305 (13.7)	972 (19.1)	333 (7.4)	<0.01
Chronic obstructive pulmonary disease	463 (4.8)	234 (4.6)	229 (5.1)	0.23
Peripheral vascular disease	175 (1.8)	122 (2.4)	53 (1.2)	<0.01
Cerebral vascular disease	237 (2.5)	115 (2.3)	122 (2.7)	0.14
Obstructive sleep apnea	417 (4.4)	273 (5.4)	144 (3.2)	<0.01
Cancer	468 (4.9)	238 (4.7)	230 (5.1)	0.29
Depression	1485 (15.5)	561 (11.0)	924 (20.6)	<0.01
Family history of coronary disease	3498 (36.6)	1738 (34.1)	1760 (39.3)	<0.01
Reason for ETT referral				
Atypical chest pain	4489 (47.0)	2386 (46.8)	2103 (47.9)	0.49
Chest pain	1679 (17.6)	835 (16.4)	844 (18.9)	<0.01
Dyspnea on exertion	862 (9.0)	453 (8.9)	409 (9.1)	0.68
Other or missing	2541 (26.5)	1288 (25.3)	1253 (28.0)	<0.01
Exercise Treadmill Variables				
Chest Pain	868 (9.1)	385 (7.6)	483 (10.8)	<0.01
Exercise Capacity <85%†	2330 (24.4)	1084 (21.3)	1246 (27.8)	<0.01
Ischemic ST segment change	1905 (19.9)	1008 (19.8)	897 (20.0)	0.77
Heart rate recovery ≤12 bpm‡	2947 (30.8)	1486 (29.2)	1461 (32.6)	<0.01
Chronotropic incompetence <0.8	2288 (23.9)	1173 (23.0)	1115 (24.9)	0.03
Maximal heart rate	155 (142,168)	155 (142,169)	155 (142,166)	<0.01
Maximal systolic blood pressure	168 (152,182)	170 (160,188)	164 (150,180)	<0.01
Maximal diastolic blood pressure	80 (76,90)	82 (78,90)	80 (76,90)	<0.01
Ectopy in recovery§	194 (2.0)	124 (2.4)	69 (1.5)	<0.01
Medications				
Aspirin	2541 (26.6)	1531 (30.1)	1010 (22.6)	<0.01
Beta-blockers	2287 (24.0)	1258 (24.7)	1029 (23.0)	0.05
Diuretics	1819 (19.1)	780 (15.3)	1039 (23.2)	<0.01
Calcium channel blockers	658 (6.9)	335 (6.7)	323 (7.2)	0.22
ACE and/or ARB	1777 (18.6)	1091 (21.4)	686 (15.3)	<0.01
Statins	2234 (23.4)	1424 (27.9)	810 (18.1)	<0.01

Continuous variables shown as median (25^{th}, 75^{th} percentiles)

Categorical variables are shown as exact count (percent)

[*] ACE = angiotensin converting enzyme; ARB= angiotensin receptor blocker; ETT = exercise treadmill testing;

[†] Proportion of age and gender predicted METS[12, 16]

[‡] A cutoff value of 12 beats/minute or less for heart rate recovery was considered abnormal.[6]

[§] Presence of 6 or more premature ventricular beats per minute in recovery. [5]

Table 2

Adjusted Associations between ETT Variables and All-cause Mortality.

ETT Variable	All patients Hazard Ratio (95% CI)	Men Hazard Ratio (95% CI)	Women Hazard Ratio (95% CI)	P value (interaction)
Exercise capacity	2.00 (1.42–2.85)***	2.89 (1.89–4.44)***	0.99 (0.52–1.93)	<0.01
Heart rate recovery	1.71 (1.19–2.45)*	1.70 (1.09–2.65)*	1.71 (0.93–3.15)	0.96
Chest pain	0.69 (0.36–1.31)	0.64 (0.28–1.48)	0.83 (0.29–2.32)	0.78
Significant ST-segment deviations	1.10 (0.75–1.61)	1.09 (0.69–1.73)	1.12 (0.57–2.19)	0.93
Chronotropic incompetence	1.09 (0.69–1.74)	1.19 (0.69–2.07)	0.99 (0.43–2.28)	0.99

* p = 0.05

** p= 0.001

*** p= <0.0001

Adjusted for age, smoking status, ectopy in recovery, maximum heart rate, and history of: diabetes, coronary artery disease, chronic obstructive pulmonary disease, cancer, obstructive sleep apnea and family history of CAD.

Table 3

Adjusted Associations between ETT Variables and MI allowing for Competing Risk of Death.

ETT Variable	All patients Hazard Ratio (95% CI)	Men Hazard Ratio (95% CI)	Women Hazard Ratio (95% CI)	P value (interaction)
Exercise capacity	2.43 (1.69–3.49)***	2.42 (1.61–3.66)***	2.83 (1.27–6.32)*	0.64
Heart rate recovery	1.32 (0.91–1.92)	1.39 (0.91–2.11)	1.14 (0.52–2.49)	0.59
Chest pain	2.29 (1.48–3.54)**	2.09 (1.24–3.51)*	3.18 (1.37–7.36)*	0.35
Significant ST-segment deviations	1.85 (1.28–2.65)**	1.63 (1.08–2.48)*	3.11 (1.46–6.62)*	0.13
Chronotropic incompetence	1.49 (0.92–2.41)	1.29 (0.74–2.20)	2.79 (0.94–8.27)	0.04

* p = 0.05

** p= 0.001

*** p= <0.0001

Adjusted for age, smoking status, ectopy in recovery, maximum heart rate, maximum BP, and history of: diabetes, coronary artery disease, peripheral vascular disease, cancer, obstructive sleep apnea and family history of CAD.