Association of Exercise Capacity on Treadmill With Future Cardiac Events in Patients Referred for Exercise Testing

Pamela N. Peterson, MD, MSPH; David J. Magid, MD, MPH; Colleen Ross, MS; P. Michael Ho, MD, PhD; John S. Rumsfeld, MD, PhD; Michael S. Lauer, MD; Ella E. Lyons, MS; Scott S. Smith, MD; Frederick A. Masoudi, MD, MSPH

Background: Little is known about the association between exercise capacity and nonfatal cardiac events in patients referred for exercise treadmill testing (ETT). Our objective was to determine the prognostic importance of exercise capacity for nonfatal cardiac events in a clinical population.

Methods: A cohort study was performed of 9191 patients referred for ETT. Median follow-up was 2.7 years. Exercise capacity was quantified as the proportion of age- and sex-predicted metabolic equivalents achieved and categorized as less than 85%, 85% to 100%, and greater than 100%. Individual primary outcomes were myocardial infarction, unstable angina, and coronary revascularization. All-cause mortality was a secondary outcome.

Results: Patients with lower exercise capacity were more likely to be female (55.38% vs 42.62%); to have comorbidities such as diabetes (23.16% vs 9.61%) and hypertension (59.43% vs 44.05%); and to have abnormal ETT findings such as chest pain on the treadmill (12.09% vs 7.63%), abnormal heart rate recovery (82.74% vs 64.13%), and abnormal chronotropic index (32.89% vs 12.20%). In multivariable analysis, including other ETT variables, lower exercise capacity (<85% of predicted) was associated with increased risk of myocardial infarction (hazard ratio [HR], 2.36; 95% confidence interval [CI], 1.55-3.60), unstable angina (HR, 2.39; 95% CI, 1.78-3.21), coronary revascularization (HR, 1.75; 95% CI, 1.46- 2.08), and all-cause mortality (HR, 2.90; 95% CI, 1.88-4.47) compared with exercise capacity greater than 100% of predicted.

Conclusion: Adjusting for patient characteristics and other ETT variables, reduced exercise capacity was associated with both nonfatal cardiovascular events and mortality in patients referred for ETT.

Arch Intern Med. 2008;168(2):174-179

Author Affiliations: Division of Cardiology, Department of Medicine, Denver Health Medical Center, Denver, Colorado (Drs Peterson and Masoudi); Division of Cardiology, Department of Medicine, University of Colorado at Denver and Health Sciences Center (Drs Peterson, Ho, Rumsfeld, and Masoudi); Clinical Research Unit (Drs Peterson, Magid, Ho, Rumsfeld, and Masoudi and Mss Ross and Lyons) and Department of Internal Medicine (Dr Smith), Kaiser Permanente of Colorado, Denver; Division of Cardiology, Department of Medicine, Denver Veterans Affairs Medical Center (Drs Ho and Rumsfeld); and Cleveland Clinic Foundation, Cleveland, Ohio (Dr Lauer).

EXERCISE TREADMILL TESTING (ETT) is noninvasive, relatively inexpensive, and commonly performed in clinical practice and provides substantial diagnostic and prognostic information. Exercise capacity is one of many important prognostic factors measured during ETT. However, while exercise capacity is predictive of mortality in epidemiologic studies of healthy women,[1,2] asymptomatic populations with cardiac risk factors,[3,4] and populations with existing cardiovascular disease,[5,6] the prognostic significance of exercise capacity in a population referred for clinical reasons has not been well studied.

Furthermore, little is known about the association between exercise capacity among patients referred for ETT and nonfatal cardiac events. Thus, when an ETT is interpreted in clinical practice, it is not clear whether poor exercise capacity simply reflects the presence of more comorbidities and worse overall health status or is a specific marker for adverse nonfatal cardiovascular outcomes. Previous studies suggest a relationship between exercise capacity and cardiovascular mortality; however, these studies have all been performed in asymptomatic nonclinical populations.[4,7-11] In addition, these studies have typically not accounted for the broader range of exercise testing measures with known prognostic significance, such as heart rate recovery and chronotropic index.[12,13] In light of the prognostic value of other ETT measures, it is important to understand the relative clinical importance of exercise capacity in predicting outcomes in patients referred for testing. Whether exercise capacity is related to nonfatal events alone, and whether such a relationship is independent of a wide range of other predictive exercise variables, remains unclear.

The aim of this study was to determine the prognostic importance of exercise capacity for nonfatal cardiac events independent of traditional treadmill measures among patients referred for ETT for clinical reasons. Specifically, we evaluated the association between the proportion of the age- and sex-predicted metabolic equivalents (METs) achieved on ETT and the risk of subsequent separate outcomes of myocardial infarction, unstable angina, and coronary revascularization procedures, adjusting for other important ETT measures.

METHODS

POPULATION

The study population consisted of consecutive patients, referred for clinical reasons, who underwent ETT between July 1, 2001, and June 30, 2004. Reasons for referral included atypical chest pain (46.94%), chest pain (17.56%), dyspnea on exertion (9.01%), preoperative screening (10.24%), risk stratification (6.96%), and other reasons (9.29%). All patients were enrolled in Kaiser Permanente of Colorado (KPCO), an integrated, nonprofit managed care organization that provides medical services to more than 480 000 members in the Denver, Colorado, metropolitan area.

Before exercise testing, a structured history and medical record review was performed to document symptoms, medical history, medication use, cardiac risk factors, and previous cardiac events and procedures. All clinical and exercise data were compiled in an electronic database. Additional comorbidity data (eg, cerebrovascular and peripheral vascular disease) were obtained from the KPCO administrative databases. For patients undergoing multiple treadmill tests during this period, only the first treadmill test was considered in the analyses.

EXERCISE TREADMILL TESTING

Exercise treadmill testing was performed according to standardized protocols, with the standard Bruce protocol used in 85% of tests. Patients were encouraged to exercise as long as possible, and achieving target heart rate alone was not used as justification for terminating exercise. Testing was symptom limited and was terminated if patients reported limiting symptoms of dyspnea, fatigue, and chest pain or for medical reasons including ischemic ST-segment changes, abnormal blood pressure response to exercise, or ventricular ectopy. Most tests (95%) were terminated for fatigue.

Peak exercise capacity was measured as the percentage of age- and sex-predicted METs achieved. The METs reflect the estimated maximal oxygen uptake for a given workload, where 1 MET is equal to the basal rate of oxygen consumption when a person is at rest (3.5 mL/kg of body weight per minute for an average adult).[14] Achieved METs were determined from the final speed and grade of the treadmill.[15] Because maximal oxygen uptake, and thus METs achieved, is strongly related to age and sex,[16] exercise capacity was calculated as the proportion of predicted METs achieved accounting for patient age and sex. The predicted exercise capacity for each patient was determined by means of the following previously published formulas: for women, predicted METs = 14.7 − (0.13 × age); and for men, predicted METs = 14.7 − (0.11 × age).[17,18] The proportion of predicted exercise capacity achieved by each individual was then calculated by dividing the METs achieved during exercise by the predicted METs, where 100% indicates a peak workload equal to that predicted for an individual based on his or her age and sex.

Several additional exercise treadmill variables were collected. Heart rate recovery was defined as the decrease in heart rate between peak exercise and 1 minute in recovery. A cutoff value of 22 beats/min or less for heart rate recovery was considered abnormal.[16,19] Chronotropic incompetence was considered present if less than 80% of a patient's heart rate reserve (calculated as [220 − age] − resting heart rate) was achieved at peak exercise for those not receiving β-blocker therapy. For those who had received β-blocker therapy within 72 hours of testing, a value of less than 62% was used to define chronotropic incompetence.[13,16] Frequent ventricular ectopy in recovery was defined as the presence of 6 or more premature ventricular beats per minute in recovery.

EVENTS AND FOLLOW-UP

The primary outcomes of interest were time from index treadmill testing to hospitalization for myocardial infarction, hospitalization for unstable angina, and time to coronary revascularization procedures, defined either as coronary artery bypass graft surgery or percutaneous coronary intervention. Hospitalizations were identified by means of the principal discharge diagnosis *International Classification of Diseases, Ninth Revision* codes of 410.x (for acute myocardial infarction) and 411.x (for unstable angina). Hospitalizations outside the managed care organization were identified in the administrative claims data. Data on coronary revascularization procedures were obtained from the KPCO administrative databases, which capture procedures performed at managed care organization contract and noncontract facilities.

The secondary outcome of interest was time to death from all causes. All-cause mortality was ascertained from KPCO databases and validated by comparison with death certificates registered with the state of Colorado. Follow-up and vital status information was available after the exercise test on 99% of the subjects through April 15, 2006.

STATISTICAL ANALYSIS

Patients were categorized into 3 groups according to proportion of predicted METs achieved. Because previous literature suggests that a functional capacity less than 85% of predicted indicates significant mortality risk[17] and because a functional capacity below 100% of predicted indicates impairment relative to one's sex and age group, the following categories of exercise capacity were used: group 1, less than 85% of predicted METs achieved; group 2, 85% to 100% of predicted METs achieved; and group 3, greater than 100% of predicted METs achieved. Baseline demographic factors, comorbidities, and exercise variables were compared across levels of exercise tolerance by the χ^2 test for categorical variables and Wilcoxon rank sum scores for continuous variables.

To define the prognostic importance of exercise capacity during ETT, freedom from myocardial infarction, unstable angina, and revascularization was compared across levels of the percentage of predicted METs achieved by means of the Kaplan-Meier method. The differences in event rates were evaluated with the log-rank test. To determine the independent association of exercise capacity with nonfatal cardiac events and all-cause mortality, multivariable Cox proportional hazards analyses were constructed for each end point. For all models, age, sex, exercise capacity, indication for treadmill testing, and all other treadmill variables were forced into the model. Variables significantly related to the outcome in bivariate analyses (based on $P < .05$) were then added to the model. Subsequently, to obtain the best-fitting models, model reduction was performed after assessing the model at each step, removing nonsignificant variables one at a time (based on $P > .10$) except for those forced into the model. The referent group for all models was the group with an exercise capacity exceeding 100% of predicted. Deaths were censored in the analyses of nonfatal car-

Table 1. Baseline Characteristics of the Study Population According to Proportion of Age- and Sex-Predicted METs Achieved[a]

Characteristic	% of Predicted METs Achieved < 85 (n=1952)	85-100 (n=2140)	> 100 (n=5099)	*P* Value[b]
METs, median (25th-75th percentile)	6 (5-7)	8 (6-8)	10 (8-11)	<.001
Age, median (25th-75th percentile), y	54 (46-65)	54 (47-63)	57 (50-67)	<.001
BMI, median (25th-75th percentile)	31.6 (27.5-36.5)	29.4 (26.4-32.9)	27.0 (24.6-29.8)	<.001
Male sex	871 (44.62)	1084 (50.65)	2926 (57.38)	<.001
Current smoking	422 (21.62)	368 (17.20)	504 (9.88)	<.001
Diabetes mellitus	452 (23.16)	338 (15.79)	490 (9.61)	<.001
Hypertension	1160 (59.43)	1067 (49.86)	2246 (44.05)	<.001
CHF	64 (3.28)	36 (1.68)	54 (1.06)	<.001
Coronary artery disease	289 (14.81)	278 (12.99)	691 (13.55)	.22
Noncoronary vascular disease	121 (6.20)	74 (3.46)	166 (3.26)	<.001
Cancer	108 (5.53)	90 (4.21)	252 (4.94)	.14
COPD	191 (9.78)	105 (4.91)	146 (2.86)	<.001
Obstructive sleep apnea	150 (7.68)	84 (3.93)	170 (3.33)	<.001
Lipid disease	1202 (61.58)	1344 (62.80)	3300 (64.72)	.03
History of depression	413 (21.16)	357 (16.68)	672 (13.18)	<.001
Exercise treadmill variables				
Chest pain, any	236 (12.09)	208 (9.72)	389 (7.63)	<.001
ST-segment change, any	385 (19.72)	403 (18.83)	1025 (20.10)	.46
Abnormal heart rate recovery, ≤ 22 beats/min	1615 (82.74)	1545 (72.20)	3270 (64.13)	<.001
Frequent ventricular ectopy in recovery	36 (1.84)	41 (1.92)	103 (2.02)	.88
Chronotropic index < 80%[c]	642 (32.89)	502 (23.46)	622 (12.20)	<.001

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; METs, metabolic equivalents.

[a]Values are given as number (percentage) unless otherwise specified.

[b]By χ^2 test (categorical variables) or Wilcoxon rank-sum score (continuous variables).

[c]Less than 62% for those receiving β-blockers within 72 hours of exercise treadmill testing.

diac events. Using percentage of predicted METs as the predictor variable, the Cox proportional hazards assumption was verified for all proportional hazards models by calculating and graphing Schoenfeld residuals by survival time.[20]

The relationship between exercise capacity and nonfatal cardiac events was also explored among prespecified subgroups including age, sex, the presence or absence of ST-segment changes during the treadmill test, the presence or absence of chest pain during the treadmill test, β-blocker use before treadmill testing, and previous coronary artery disease. We constructed multivariable Cox proportional hazards models by using the same multivariable modeling approach as the primary risk models, stratified by each of the prespecified subgroups. The statistical significance of differences among strata was tested with 2-way interaction terms in full models. Finally, we explored whether the relationships between exercise capacity and outcomes were linear or whether threshold points existed. Restricted cubic splines were fit by means of the proportion of predicted METs achieved with all nonfatal cardiac outcomes in survival analyses with an iterative examination of hazard ratios and *P* values to determine possible points of inflection in the relationship.

The study was approved by the KPCO Institutional Review Board. All analyses were performed with the SAS statistical package version 9.1 (SAS Institute Inc, Cary, North Carolina).

RESULTS

Baseline characteristics of the study population are presented in **Table 1**. Patients with lower exercise capacity were more often female and had a higher prevalence of comorbid conditions such as diabetes mellitus and hypertension compared with those with greater exercise capacity. In addition, patients with reduced exercise capacity were more likely to have chest pain with exercise, ST-segment changes, an abnormal heart rate recovery, and an abnormal chronotropic index during ETT.

The median length of follow-up was 2.7 years. During that time, 119 hospitalizations for myocardial infarction, 259 hospitalizations for unstable angina, 749 revascularization procedures (percutaneous coronary intervention or coronary artery bypass graft surgery), and 132 deaths occurred. In Kaplan-Meier analysis, the rate of myocardial infarction was greater for lower levels of predicted exercise capacity (log-rank $P<.001$ across levels of exercise capacity, **Figure 1**A). Similarly, the rate of unstable angina and coronary revascularization was greater for lower levels of exercise capacity (log-rank $P\leq.001$ for both outcomes, Figure 1B and C). After adjusting for demographic, clinical, and treadmill variables, the failure to reach 85% of predicted exercise capacity remained significantly associated with an increased risk of myocardial infarction (hazard ratio [HR], 2.36; 95% confidence interval [CI], 1.55-3.60), unstable angina (HR, 2.39; 95% CI, 1.78-3.21), and coronary revascularization (HR, 1.75; 95% CI, 1.46- 2.08) (**Table 2**) compared with those who achieved greater than 100%. For those achieving between 85% and 100% of predicted exercise capacity, there was not a significant increase in risk of nonfatal outcomes compared with those who achieved greater than 100% of their predicted exercise capacity.

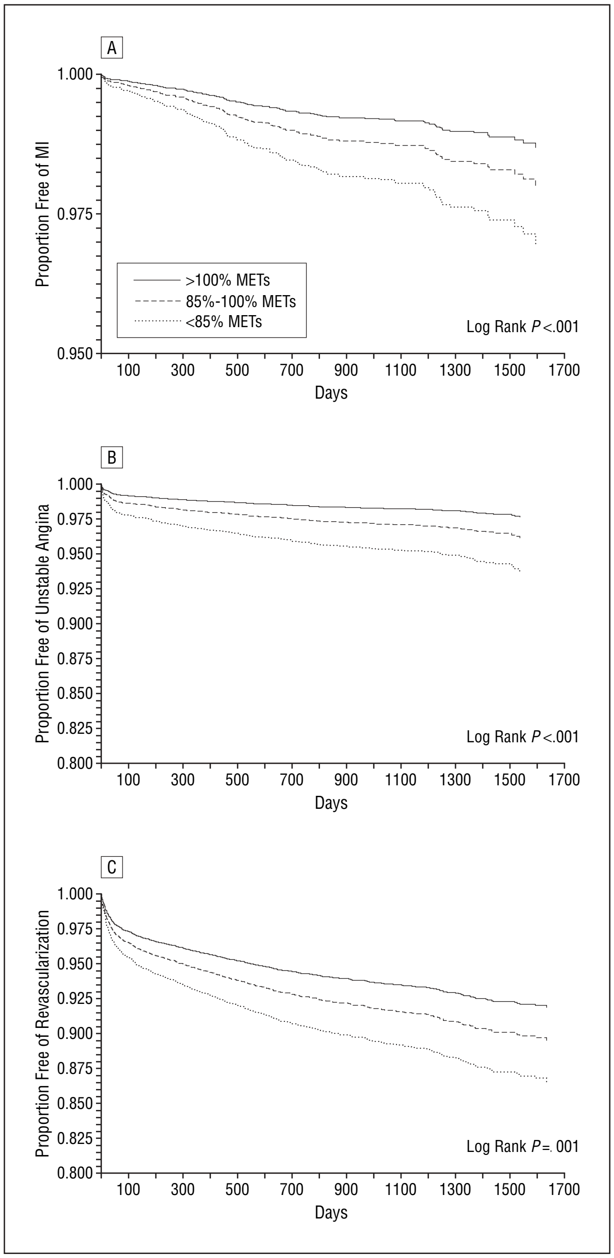

Figure 1. Kaplan-Meier curves of freedom from nonfatal cardiac events according to proportion of age- and sex-predicted metabolic equivalents (METs) achieved. A, Myocardial infarction (MI); B, unstable angina; and C, revascularization.

In fully adjusted models, exercise capacity was significantly associated with increased risk of all-cause mortality (HR, 2.90; 95% CI, 1.88-4.47) for those who achieved less than 85% compared with those who achieved greater than 100% of age- and sex-predicted exercise capacity (Table 2). Achieving 85% to 100% of predicted exercise capacity was also significantly associated with increased risk of all-cause mortality (HR, 1.78; 95% CI, 1.13-2.81) compared with those who achieved greater than 100% of their predicted exercise capacity.

We also performed stratified analyses according to age, sex, the presence or absence of ST-segment changes during the treadmill test, chest pain during the treadmill test, β-blocker use before treadmill testing, and previous coronary artery disease. The association between exercise capacity and myocardial infarction (**Figure 2**), unstable angina, and revascularization were consistent regardless of the patient subgroup evaluated (results for unstable angina and revascularization not shown). Formal tests for interactions were not statistically significant for any subgroup. Finally, for all nonfatal cardiac outcomes, the nonlinear components of restricted cubic splines were not significant, indicating that the relationship between exercise capacity and nonfatal cardiac events was linear.

Table 2. Prediction of Outcomes by Proportion of Age- and Sex-Predicted METs Achieved by Cox Proportional Hazards Analysis

Outcome, % of Predicted METs Achieved	No. of Patients	HR (95% CI) Crude	HR (95% CI) Adjusted
Myocardial infarction[a]	119		
< 85	49	2.36 (1.60-3.49)	2.36 (1.55-3.60)
85-100	18	0.78 (0.46-1.34)	0.79 (0.46-1.36)
> 100	52	1 [Reference]	1 [Reference]
Unstable angina[b]	259		
< 85	101	2.69 (2.03-3.55)	2.39 (1.78-3.21)
85-100	61	1.46 (1.06-2.01)	1.31 (0.94-1.81)
> 100	97	1 [Reference]	1 [Reference]
CABG, PCI[c]	749		
< 85	228	1.72 (1.46-2.03)	1.75 (1.46-2.08)
85-100	172	1.15 (0.96-1.38)	1.08 (0.90-1.31)
> 100	349	1 [Reference]	1 [Reference]
Mortality, all-cause[d]	132		
< 85	52	2.72 (1.80-4.04)	2.90 (1.88-4.47)
85-100	33	1.57 (1.01-2.45)	1.78 (1.13-2.81)
> 100	47	1 [Reference]	1 [Reference]

Abbreviations: CABG, coronary artery bypass grafting; CI, confidence interval; HR, hazard ratio; METs, metabolic equivalents; PCI, percutaneous coronary intervention.

[a] Adjusted for chest pain, ST-segment changes, heart rate recovery, chronotropic index, ventricular ectopy, indication for exercise treadmill testing, age, sex, history of coronary artery disease, smoking, cancer, and chronic obstructive pulmonary disease.

[b] Adjusted for chest pain, ST-segment changes, heart rate recovery, chronotropic index, ventricular ectopy, indication for exercise treadmill testing, age, sex, diabetes, history of coronary artery disease, lipid disorder, statin use, and β-blocker use.

[c] Adjusted for chest pain, ST-segment changes, heart rate recovery, chronotropic index, ventricular ectopy, indication for exercise treadmill testing, age, sex, diabetes, history of coronary artery disease, lipid disorder, statin use, β-blocker use, and angiotensin-converting enzyme or angiotensin receptor blocker use.

[d] Adjusted for chest pain, ST-segment changes, heart rate recovery, chronotropic index, ventricular ectopy, indication for exercise treadmill testing, age, sex, body mass index, chronic obstructive pulmonary disease, diabetes, and cancer.

COMMENT

The objective of this study was to determine the prognostic value of exercise capacity measured from ETT for future nonfatal cardiac events among patients referred for clinical indications. We found that patients with a decreased exercise capacity had an increased risk of myocardial infarction, unstable angina, and coronary revascularization. In addition, failure to reach 85% of predicted METs was associated with a higher risk of death from all causes.

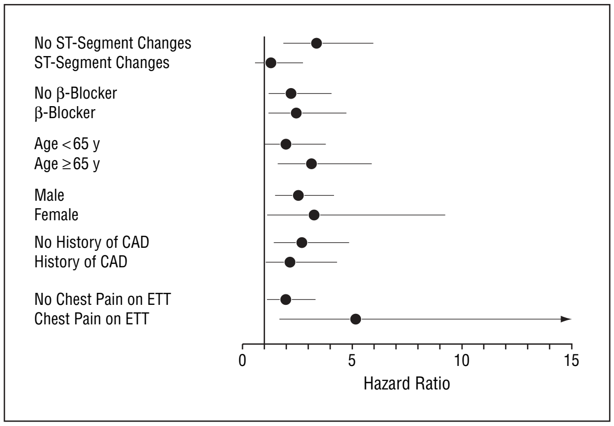

Figure 2. Association (shown as hazard ratio and 95% confidence interval) between exercise capacity and hospitalization for myocardial infarction among patient subgroups for those who achieved less than 85% compared with those who achieved greater than 100% of age- and sex-predicted exercise capacity. CAD indicates coronary artery disease; ETT, exercise treadmill testing.

Few studies have focused on exercise capacity as a prognostic factor for future nonfatal cardiac events in a clinical population. Previous studies in patients referred for ETT found that higher levels of exercise capacity provided additional information about the combined risk of cardiac events and cardiovascular death[21,22] but did not assess nonfatal cardiac outcomes separately. Furthermore, these studies did not adjust for the ETT measures of heart rate recovery or chronotropic index, which are independent predictors of outcomes after ETT.[12,13] Multiple ETT variables have prognostic significance and should be used clinically in a comprehensive ETT assessment of prognosis.[16] Therefore, these variables should be considered when the additional prognostic value of exercise capacity is evaluated. The results of our study expand the current literature by demonstrating the prognostic value of exercise capacity for nonfatal cardiac events as separate end points and independent of other exercise testing measures in populations referred for ETT.

Patients with poor exercise capacity are often considered to have an overall poor prognosis, but the reasons for this risk may be unclear. For example, poor exercise capacity could be attributed to other comorbidities, such as chronic lung disease, arthritis, or other musculoskeletal conditions, and it might be assumed that future adverse outcomes are related to such comorbid conditions. In the absence of other treadmill indicators, such as chest pain or ST-segment changes, clinicians may underestimate the risk of future cardiovascular morbidity in patients with poor exercise capacity. This study found that, independent of ST-segment deviations, symptoms of chest pain, and comorbidities, patients with lower levels of exercise capacity are at increased risk of subsequent cardiovascular events. Thus, exercise capacity should be considered an important indicator of cardiovascular risk rather than simply a less specific surrogate for a greater burden of comorbidity.

This study also corroborates and extends the findings of previous studies that identify reduced exercise capacity as a risk factor for mortality. Others have demonstrated that exercise capacity is related to all-cause mortality in patients undergoing stress testing after myocardial infarction,[5] before coronary bypass surgery,[6] and in healthy populations of men and women.[1,2] However, none adjusted for other exercise treadmill variables, which have more recently been shown to be important prognostic factors for mortality after ETT. In contrast to previous studies, we were able to demonstrate the independent role of exercise capacity.

Poor exercise capacity may be useful to identify high-risk patients who may benefit from therapeutic interventions. While prospective studies are needed to determine the best diagnostic and therapeutic approaches for these patients, aggressive risk factor modification and close follow-up should be considered to reduce the risk of future cardiac events. Furthermore, previous evidence suggests that physical activity reduces the risk of adverse outcomes.[23,24] Exercise treadmill testing may provide an opportunity for clinicians to motivate sedentary patients to increase their level of physical activity.[25]

It is important to emphasize that, in contrast to previous epidemiologic studies that assessed the prognostic importance of exercise capacity in relatively unselected populations, this study focused on the implications of decreased exercise capacity when ETT was performed for clinical indications. Thus, while this study should not be used to make general statements about the prognostic importance of exercise capacity in the general population, it is useful for informing decision making for patients referred for ETT. Given the frequency with which ETT is performed annually in the United States in populations similar to those included in this study, the findings have broad clinical relevance.

Other factors should be considered in the interpretation of these results. First, exercise capacity was estimated on the basis of the speed and degree of incline of the treadmill and not directly measured by ventilatory gas exchange.[26] However, achieved METs are standardized and are a more common and practical objective measure of exercise capacity in clinical practice. Second, outcomes of unstable angina and myocardial infarction were determined by means of *International Classification of Diseases, Ninth Revision* codes, which may result in misclassification. Third, because the study population derived from a single managed care organization, these results may not apply to other populations. However, it was a health care–based study of a large integrated health care delivery organization, and all treadmill tests performed between July 1, 2001, and June 30, 2004, were prospectively captured in this database. Fourth, because the data were unavailable, we were unable to adjust for socioeconomic status or for race. Finally, the results may be affected by unmeasured confounding. However, a large number of covariates were included in the multivariate models, including comorbid conditions and extensive treadmill variables.

In summary, exercise capacity was a strong and independent factor associated with nonfatal cardiac events and mortality in a health care–based cohort of patients referred for ETT. The association with nonfatal cardiac events suggests that poor exercise capacity is not simply a reflection of a greater burden of comorbidities and worse patient health status. This study has important implications for the identification of patients at high risk for future cardiovascular morbidity and suggests that aggressive risk factor modification and close follow-up should be considered for patients with impaired exercise capacity. Prospective intervention studies are needed to determine the best diagnostic and therapeutic approaches for this patient population.

Accepted for Publication: August 31, 2007.
Correspondence: Pamela N. Peterson, MD, MSPH, Division of Cardiology, Department of Medicine, Denver Health Medical Center, Mail Code 0960, 777 Bannock St, Denver, CO 80204 (Pamela.Peterson@uchsc.edu).
Author Contributions: Dr Peterson had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Peterson, Magid, Lauer, Smith, and Masoudi. *Acquisition of data:* Magid, Ross, and Lyons. *Analysis and interpretation of data:* Magid, Ross, Ho, Rumsfeld, Lauer, Lyons, and Masoudi. *Drafting of the manuscript:* Peterson, Lyons, and Masoudi. *Critical revision of the manuscript for important intellectual content:* Magid, Ross, Ho, Rumsfeld, Lauer, Smith, and Masoudi. *Statistical analysis:* Peterson, Ross, Lyons, and Masoudi. *Obtained funding:* Magid. *Administrative, technical, and material support:* Magid and Lauer. *Study supervision:* Magid.
Financial Disclosure: None reported.
Funding/Support: This study was funded in part by CV Therapeutics Inc.
Role of the Sponsor: CV Therapeutics Inc was not directly involved in the design and conduct of the study, or in the collection, management, analysis, or interpretation of the data. This sponsor was not involved in the preparation, revision, or approval of the manuscript.
Additional Information: The data analysis, including housing of the entire raw data set, study protocol, and the prespecified plan for data analysis, was conducted at the Kaiser Permanente of Colorado Clinical Research Unit.

REFERENCES

1. Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. *N Engl J Med*. 2002;346(11):793-801.
2. Gulati M, Pandey DK, Arnsdorf MF, et al. Exercise capacity and the risk of death in women: the St James Women Take Heart Project. *Circulation*. 2003;108(13):1554-1559.
3. Wei M, Gibbons LW, Kampert JB, Nichaman MZ, Blair SN. Low cardiorespiratory fitness and physical inactivity as predictors of mortality in men with type 2 diabetes. *Ann Intern Med*. 2000;132(8):605-611.
4. Church TS, Kampert JB, Gibbons LW, Barlow CE, Blair SN. Usefulness of cardiorespiratory fitness as a predictor of all-cause and cardiovascular disease mortality in men with systemic hypertension. *Am J Cardiol*. 2001;88(6):651-656.
5. Domínguez H, Torp-Pedersen C, Koeber L, Rask-Madsen C. Prognostic value of exercise testing in a cohort of patients followed for 15 years after acute myocardial infarction. *Eur Heart J*. 2001;22(4):300-306.
6. Weiner DA, Ryan TJ, McCabe CH, et al. The role of exercise testing in identifying patients with improved survival after coronary artery bypass surgery. *J Am Coll Cardiol*. 1986;8(4):741-748.
7. Snader CE, Marwick TH, Pashkow FJ, Harvey SA, Thomas JD, Lauer MS. Importance of estimated functional capacity as a predictor of all-cause mortality among patients referred for exercise thallium single-photon emission computed tomography: report of 3,400 patients from a single center. *J Am Coll Cardiol*. 1997;30(3):641-648.
8. Ekelund LG, Haskell WL, Johnson JL, Whaley FS, Criqui MH, Sheps DS. Physical fitness as a predictor of cardiovascular mortality in asymptomatic North American men: the Lipid Research Clinics Mortality Follow-up Study. *N Engl J Med*. 1988;319(21):1379-1384.
9. Mora S, Redberg RF, Cui Y, et al. Ability of exercise testing to predict cardiovascular and all-cause death in asymptomatic women: a 20-year follow-up of the Lipid Research Clinics Prevalence Study. *JAMA*. 2003;290(12):1600-1607.
10. Church TS, LaMonte MJ, Barlow CE, Blair SN. Cardiorespiratory fitness and body mass index as predictors of cardiovascular disease mortality among men with diabetes. *Arch Intern Med*. 2005;165(18):2114-2120.
11. Gibbons LW, Mitchell TL, Wei M, Blair SN, Cooper KH. Maximal exercise test as a predictor of risk for mortality from coronary heart disease in asymptomatic men. *Am J Cardiol*. 2000;86(1):53-58.
12. Nishime EO, Cole CR, Blackstone EH, Pashkow FJ, Lauer MS. Heart rate recovery and treadmill exercise score as predictors of mortality in patients referred for exercise ECG. *JAMA*. 2000;284(11):1392-1398.
13. Lauer MS, Francis GS, Okin PM, Pashkow FJ, Snader CE, Marwick TH. Impaired chronotropic response to exercise stress testing as a predictor of mortality. *JAMA*. 1999;281(6):524-529.
14. Jetté M, Sidney K, Blümchen G. Metabolic equivalents (METS) in exercise testing, exercise prescription, and evaluation of functional capacity. *Clin Cardiol*. 1990;13(8):555-565.
15. Bruce RA, Kusumi F, Hosmer D. Maximal oxygen intake and nomographic assessment of functional aerobic impairment in cardiovascular disease. *Am Heart J*. 1973;85(4):546-562.
16. Kligfield P, Lauer MS. Exercise electrocardiogram testing: beyond the ST segment. *Circulation*. 2006;114(19):2070-2082.
17. Gulati M, Black HR, Shaw LJ, et al. The prognostic value of a nomogram for exercise capacity in women. *N Engl J Med*. 2005;353(5):468-475.
18. Morris CK, Myers J, Froelicher VF, Kawaguchi T, Ueshima K, Hideg A. Nomogram based on metabolic equivalents and age for assessing aerobic exercise capacity in men. *J Am Coll Cardiol*. 1993;22(1):175-182.
19. Shetler K, Marcus R, Froelicher VF, et al. Heart rate recovery: validation and methodologic issues. *J Am Coll Cardiol*. 2001;38(7):1980-1987.
20. Cox D. Regression models and life tables. *J R Stat Soc B*. 1972;34:187-220.
21. Roger VL, Jacobsen SJ, Pellikka PA, Miller TD, Bailey KR, Gersh BJ. Prognostic value of treadmill exercise testing: a population-based study in Olmsted County, Minnesota. *Circulation*. 1998;98(25):2836-2841.
22. Goraya TY, Jacobsen SJ, Pellikka PA, et al. Prognostic value of treadmill exercise testing in elderly persons. *Ann Intern Med*. 2000;132(11):862-870.
23. Mark DB, Lauer MS. Exercise capacity: the prognostic variable that doesn't get enough respect. *Circulation*. 2003;108(13):1534-1536.
24. Warburton DER, Nicol CW, Bredin SSD. Health benefits of physical activity: the evidence. *CMAJ*. 2006;174(6):801-809.
25. Andersen RE, Blair SN, Cheskin LJ, Bartlett SJ. Encouraging patients to become more physically active: the physician's role. *Ann Intern Med*. 1997;127(5):395-400.
26. Myers J, Buchanan N, Walsh D, et al. Comparison of the ramp versus standard exercise protocols. *J Am Coll Cardiol*. 1991;17(6):1334-1342.