Diagnostic exercise tests on 4000 consecutive men

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Objective Our purpose was to report the prevalence of abnormal treadmill test responses and their association with mortality in a large consecutive series of patients referred for standard diagnostic exercise tests, with testing performed and reported in a standardized fashion.

Background Exercise testing is widely performed, but an analysis of responses has not been presented for a large number of consecutive tests performed on patients referred for diagnosis of cardiac disease.

Methods All patients referred for evaluation at 2 university-affiliated Veterans Affairs Medical Centers who underwent exercise treadmill tests for clinical indications between 1987 and 2000 were determined to be dead or alive according to the Social Security Death Index after a mean 5.9-year follow-up. Patients with established heart disease (ie, prior coronary bypass surgery, myocardial infarction, or congestive heart failure) were excluded from analyses. Clinical and exercise test variables were collected prospectively according to standard definitions; testing and data management were performed in a standardized fashion with a computer-assisted protocol. All-cause mortality was used as the end point for follow-up. Standard survival analysis was performed, including Kaplan-Meier curves and a Cox hazard model.

Results After the exclusions, 3974 men (mean age 57.5 ± 11 years) had standard diagnostic exercise testing over the study period with a mean of 5.9 (±3.7) years of follow-up (64% of all tested). There were no complications of testing in this clinically referred population, 82% of whom were referred for chest pain, risk factors, or signs and symptoms of ischemic heart disease. Five hundred forty-nine (14%) had a history of typical angina. Indications for testing were in accordance with published guidelines. A total of 545 died, yielding an annual mortality rate of 1.8%. The Cox hazard model chose the following variables in rank order as independently associated with time to death: change in rate pressure product, age greater than 65 years, METs less than 5, and electrocardiographic left ventricular hypertrophy. A score based on these variables classified patients into low-, medium-, and high-risk groups. The high-risk group with a score greater than 3 has a hazard ratio of 4 (95% confidence interval 3.82-4.27) and an annual mortality rate of 4%.

Conclusion This comprehensive analysis provides rates of various abnormal responses that can be expected in men referred for diagnostic exercise testing at typical Veterans Administration Medical Centers. Four simple variables combined as a score predict all-cause mortality after clinical decisions for therapy are prescribed. (Am Heart J 2001;142:127-35.)

All the guidelines relative to ischemic heart disease recommend the standard exercise test as the first choice for the evaluation of the patient with chest pain who does not have resting electrocardiographic (ECG) abnormalities that affect the interpretation of the exercise ECG response.[1,2] In this report we focus on patients referred mainly for diagnosis of coronary artery disease and exclude patients who had existing cardiac diagnoses. The results can be used to provide the prevalence of unusual responses such as ST elevation, exertional hypotension, bundle branch block, and ventricular tachycardia. Such prevalence data can be helpful in the development of competency statements because it highlights what those who perform exercise tests should know.[3] In addition, the Social Security Death Index data now readily available on the World Wide Web make it possible to evaluate predictors of all-cause mortality. The purpose of the current study was to report the prevalence and descriptive statistics of treadmill test responses and their association with mortality in a large consecutive series of patients referred for diagnostic exercise tests with testing performed and reported in a standardized fashion. A previous report included those with heart disease,[4] whereas here we consider the diagnostic subset of the entire population.

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4/1/115795
doi:10.1067/mhj.2001.115795

Methods

Population

More than 6000 consecutive male veterans underwent testing at 2 clinical exercise laboratories (Long Beach VA 1987-1991, Palo Alto VA 1992-2000) directed by 2 of the authors (V. F. F. and J. M.) who implemented a standardized method. Patients who were subjects in research protocols were not considered in the analyses. Thirty-six percent of the patients, those with known heart disease, were removed from analysis, to leave the target population of 3974.

Data collection

No imaging modality was performed in conjunction with the tests; however, expired gases were measured in approximately one fifth of subjects. Both laboratories had affiliations with universities and had academic medical staffs with rotating house officers and fellows. All tests were supervised directly by these physicians or by nurse practitioners; all tests were over read by 2 of the authors (V. F. F. and J. M.). A thorough clinical history, listing of medications, and risk factors were recorded prospectively at the time of exercise treadmill testing by use of computerized forms beginning in 1987.[5,6] The forms included standard definitions of clinical conditions and exercise responses.

Exercise testing

Patients underwent symptom-limited treadmill testing with the United States Air Force School of Aerospace Medicine[7] protocol or an individualized ramp treadmill protocol that achieved similar hemodynamic responses.[8] Before ramp testing, the patients were given a questionnaire to estimate their exercise capacity; this allowed most patients to reach maximal exercise within the recommended range of 8 to 12 minutes.[9] Heart rate targets were not used as an end point or to judge the adequacy of the test. Patients did not perform a cool down walk but were placed supine as soon as possible after exercise.[10] Medications were not changed or stopped before testing.

Visual ST-segment depression was measured at the J junction and corrected for pre-exercise ST-segment depression while standing; the ST slope was measured over the following 60 ms and classified as upsloping, horizontal, or downsloping. The ST response considered was the most horizontal or downsloping ST-segment depression in any lead except aVR during exercise or recovery. An abnormal response was defined as 1 mm or more of horizontal or downsloping ST-segment depression. Ventricular tachycardia was defined as a run of 3 or more consecutive premature ventricular contractions (PVCs) as previously described.[11] Blood pressure was taken manually and the metabolic eqivalents or multiples of 35 $mL/O_2/kg/min$ (METs) were estimated from treadmill speed and grade. Exertional hypotension was coded as either a 10-mm Hg drop in systolic blood pressure (SBP) after a rise or a drop of 10 mm Hg below standing pretest. An exercise SBP code was considered in which 0 = increase greater than 40 mm Hg, 1 = increase 31 to 40 mm Hg, 2 = increase 21 to 30 mm Hg, 3 = increase 11 to 20 mm Hg, 4 = increase 0 to 10 mm Hg, and 5 = drop below standing pretest as previously defined.[12] Pressure rate product (PRP or double product) pretest and at maximal exercise was calculated as the product of SBP and heart rate. ΔPRP was calculated as follows: PRP at maximal exercise – PRP at rest/1000. The ST/heart rate index was calculated by dividing the amount of ST depression regardless of slope by the change in heart rate with exercise.

All 12-lead ECG signals were digitized and stored on CD-ROMs after being recorded by a Mortara E-scribe (Milwaukee, Wis) or a Burdick/Spacelabs QUEST (Milton, Wis).

No test was classified as indeterminate.[13] The exercise tests were performed, analyzed, and reported per standard protocol and with use of a computerized database (EXTRA, Mosby, Chicago, Ill).[14] The textual report was automatically downloaded into the Veterans Affairs database (DHCP or Vista) for distribution.[15]

Follow-up

The Social Security Death Index was used to match all the patients by name and social security number. The index is updated weekly and current information was used (www.ancestry.com), ensuring 100% completeness. Death status was determined for the entire sample as of July 2000.

Statistical analysis

Number Crunching System Software (Kayesville, Utah) was used for all statistical analyses after the data were transferred from an ACCESS (Microsoft) database. Unpaired *t* testing was used to compare the mean values in the 2 groups and χ^2 tests were applied for differences between proportions. Total (all-cause) mortality was used as the end point for follow-up for survival analysis. Censoring was not performed because data regarding subsequent interventions were not available for all patients. Survival analysis was performed with Kaplan-Meier curves to compare variables and cut points, and Cox hazard function was used to demonstrate which variables were independently and significantly associated with time to death. Automatic selection of variables was performed with a Z value cutoff of 2 and 20 iterations. Hazard ratios were calculated along with their 95% confidence intervals.

Results

Population demographics

This male population had a mean height of 69 inches (±4), a mean weight of 193 pounds (±38), and a mean body mass index (BMI) of 28 ± 5. The average resting heart rate was 78 ± 21 beats/min with a corresponding mean SBP of 134 ± 21 mm Hg. In the total population there were 789 (19.9%) inpatients and they had a significantly higher percentage of deaths than outpatients did (30% vs 18%, $P < .001$). Overall, 74% were white, 9% were Hispanic, and 12% were African American. There were no significant differences in survivorship among the different ethnic groups. Five hundred sixty patients (14.1%) were on β-blockers, 61 (1.5%) had a history of atrial fibrillation, and 106 (2.7%) had a history of stroke. There were 384 (9.7%) diabetic patients, 1214 (30.5%) had hypercholesterolemia, and 1841 (46.3%) had hypertension. About 30% of the population was obese with a BMI >27 and 1248 (31.4%) were smokers at the

Table I. Population characteristics that were statistically different by univariate comparison between those who died and those who survived

Variable	Total sample (n = 3974) (%)	Survived (n = 3429) (86%)	Died (n = 545) (14%)	P value
Demographics				
Age (mean ± SD) (y)	57.5 ± 11.6	56.4 ± 11.6	63.8 ± 9.4	<.001
Age ≥65 y	29.8%	26.5%	50.6%	<.001
Weight (pounds) (mean ± SD)	193.2 ± 38.8	194.4 ± 38.9	185.9 ± 37.4	<.001
Medications				
Calcium antagonists	21.5%	20.3%	29.4%	<.001
Nitrates	14%	12.4%	24%	<.001
Antihypertensives	21.6%	19.9%	32.3%	<.001
Medical history				
Claudication	4.1%	3.7%	6.4%	.004
Pulmonary disease	6%	5.4%	9.7%	<.001
Typical angina pectoris	12.9%	11.9%	19.3%	<.001
Family history of coronary artery disease	22.7%	15.6%	23.9%	<.001
Ever smoked	57.3%	59.4%	44.8%	<.001
Resting ECG abnormalities				
Abnormal ECG	23.1%	21.4%	33.8%	<.001
Right bundle branch block	3.3%	2.7%	7.2%	<.001
Left ventricular hypertrophy	4.6%	4.1%	8.1%	<.001
ST depression	5.7%	4.8%	11.6%	<.001

time of testing. There were no significant differences in the prevalence of these variables between those who died and those who survived. Those who died were significantly older (64 vs 56 years old, $P < .001$) and had a lower BMI than survivors. Although there were significant differences in other resting ECG abnormalities, the prevalence of left bundle branch block (LBBB) (22 or 0.6%) and atrial fibrillation (34 or 0.8%) did not differ according to alive/dead status. The other relevant variables that exhibited a significant difference between those who survived and the 545 who died over the mean 5.9 years follow-up are presented with significance levels in Table I. There was an average annual mortality rate of 1.8%. Most of the major medical history items and medications except for β-blockers were significantly more prevalent in those who died, including typical angina. The only risk factor for coronary disease that was significantly more prevalent in those who died was a family history of heart disease.

Reasons for testing

More than 80% of patients were tested for the diagnosis of chest pain or evaluation of signs or symptoms possibly resulting from coronary disease or for elevated risk factors. Those who survived were more likely to be tested for "softer" indications (arrhythmias, exercise capacity, dyspnea on exertion), whereas those who died were more likely to be tested for symptoms of angina.

Exercise test responses

No major complications (ie, death or infarction) were encountered at the time of testing. Exercise test responses for the entire population, and specifically for those who survived and the 545 who died, along with significance levels for differences are presented in Table II. All the major exercise ECG abnormalities were significantly more prevalent in those who died except for rate-dependent LBBB (15 or 0.4%), rate-dependent intraventricular conduction defects (43 or 1.1%), ST elevation (12 or 1.2%), occurrence of angina (386 or 9.7%), and exercise-induced ventricular tachycardia (VT) of ≥3 consecutive beats (45, 1.1%). Although angina was not more frequent during the exercise test among those who died, it was significantly more common as the reason for stopping. Abnormal exercise–induced ST depression, the most common ECG abnormality, was significantly more prevalent in those who died (27% vs 18%, $P < .001$). The next most prevalent ECG abnormality was frequent PVCs or VT (3 PVCs in a row or more), and this combined response was significantly more prevalent in those who died (6% vs 10%, $P < .001$). ST elevation was rare. Although exercise-induced ventricular conduction abnormalities were rare, exercise-induced right bundle branch block (RBBB) was significantly more common in those who died (1.4% vs 4.6%, $P < .001$). Exercise-induced hypotension was relatively rare (72, 1.8%) and not significantly more prevalent in those who died, whereas failure to reach a SBP of 130 mm Hg was more common in those who died (1.7 vs. 2.6%, $P < .001$). Both groups gave a similar effort as reflected in the mean Borg scale rating of "very hard" (rating of 17 ± 3).

The average maximum heart rate was 141 ± 24 beats/min and the corresponding SBP was 182 ± 28

Table II. Exercise test characteristics that were statistically different by univariate comparison between those who died and those who survived

Variable	Total sample (n = 3974) (%)	Survived (n = 3429) (86%)	Died (n = 545) (14%)	*P* value
Angina reason for stopping	4.4%	3.9%	7.3%	.001
Exercise-induced ST depression ≥1 mm	19.1%	17.8%	27.2%	<.001
Rate-dependent RBBB	1.9%	1.4%	4.6%	<.001
Exercise-induced arrhythmias (frequent PVCs or VT)	6.4%	5.9%	9.7%	.001
Resting hemodynamics				
SBP (mm Hg) (mean ± SD)	134 ± 21	134 ± 21	136 ± 23	<.001
Diastolic blood pressure (mm Hg) (mean ± SD)	83 ± 12	83 ± 12	81 ± 13	.007
Double product (mean ± SD × 1000)	10.5 ± 3.3	11.1 ± 2.9	10.4 ± 3.4	<.001
Maximum hemodynamics				
Heart rate (beats/min) (mean ± SD)	141 ± 24	143 ± 23	131 ± 23	<.001
Maximum heart rate <85% age predicted	43.8%	41.9%	55.6%	<.001
Maximum SBP ≤130 mm Hg	2%	1.7%	2.6%	.008
Double product (mean ± SD × 1000)	26.1 ± 6.5	26.5 ± 6.5	23.8 ± 6.5	<.001
Difference of double product (mean ± SD × 1000)	15.6 ± 6.5	16.0 ± 6.5	12.7 ± 5.9	<.001
METs	8.9 ± 4.6	9.25 ± 4.7	6.9 ± 3.8	<.001
Fewer than 5 METS	14.5%	12.6%	27.2%	<.001

Table III. Univariate comparison of individual variables with nonparametric Kaplan-Meier statistics

Variables	Total (n = 3974) (%)	Hazard ratio	95% Confidence limits	Mortality 5 y	Mortality 10 y
Age ≥65 y	29.8%	2.3	2.25-2.3	16	36
ΔPRP <20 (×1000)	24%	2.8	2.1-3.4	4	12
METs <5	14.5%	2.1	1.8-2.5	22	44
ECG left ventricular hypertrophy	4.6%	2.0	1.4-3.0	18	42
Exercise-induced ST depression ≥1 mm	19.1%	1.4	1.3-1.6	22	30
Angina occurred	9.7%	1.2	1.1-1.4	10	26
Exercise-induced arrhythmias (frequent PVCs or VT)	6.4%	1.9	1.4-2.6	14	34
Angina as a reason for stopping	4.4%	1.7	1.1-2.4	13	35
Arrhythmias as a reason for stopping	8%	1.4	1.2-1.7	16	31
Exercise-induced hypotension*	2.5%	1.2	0.7-2.2	14	33

*Rise and drop of ≥10 mm Hg or maximal exercise SBP ≥10 mm Hg less than pretest standing.

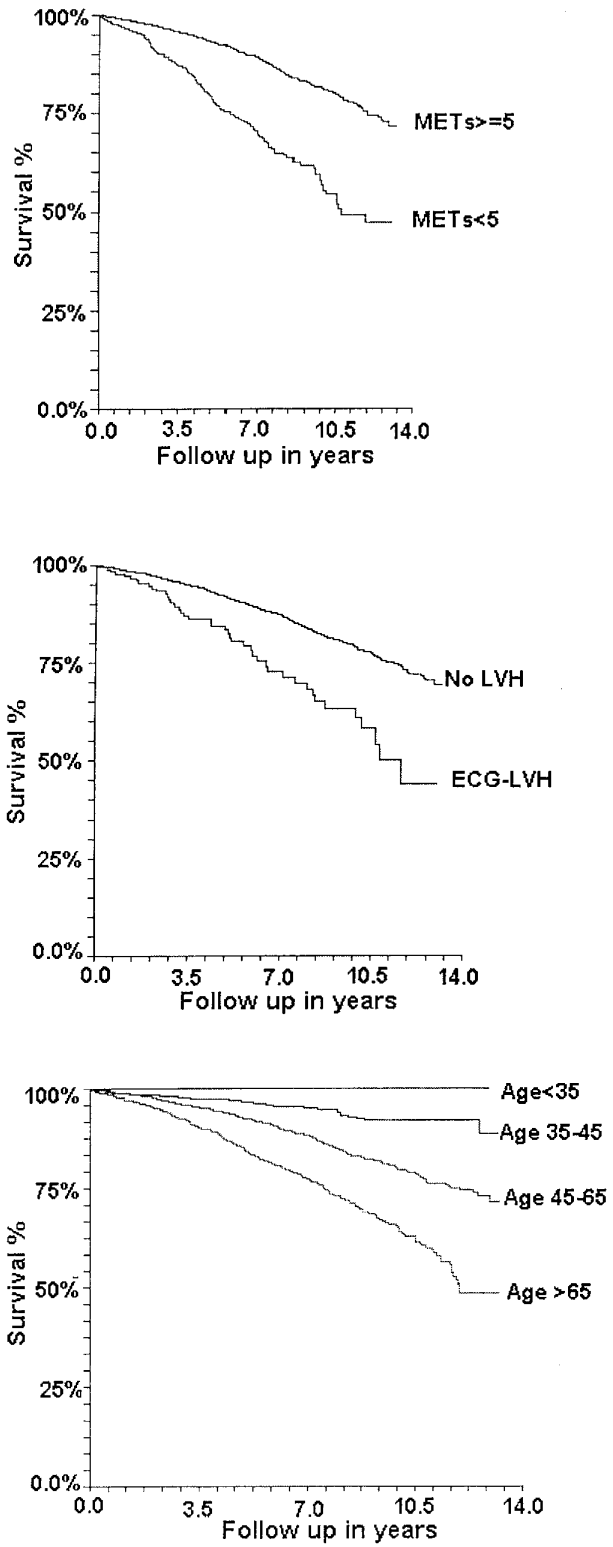
mm Hg. Failure to reach the age-predicted heart rate target occurred in half the population and was significantly more prevalent in those who died. The standing PRP, maximum PRP, and ΔPRP were significantly higher in those who survived, as were maximal heart rate, METs, and maximal SBP.

Survival analysis

The results for univariate Kaplan-Meier survival curves for selected variables are presented in Table III. The curves themselves are presented for the 3 most important measurements; Figures 1 and 2 show the results with the score for ΔPRP.

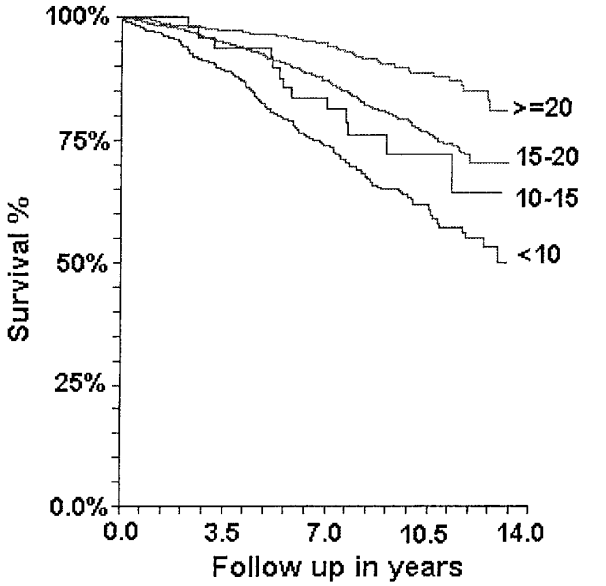
With use of stepwise selection, the proportional hazards model was allowed to build on each variable group. The clinical variables included were age, ECG left ventricular hypertrophy, history of diabetes, history of smoking, history of pulmonary disease, resting ECG abnormalities, resting ST depression, resting heart rate, resting systolic and diastolic blood pressures, and history of typical angina. Age, ECG left ventricular hypertrophy, history of diabetes, history of smoking, history of pulmonary disease, and resting ECG abnormalities were significant predictors of death roughly in that order. The exercise variables included were METs, ΔPRP, maximum PRP, exercise-induced frequent PVCs or VT, exercise-induced ST depression, exercise-induced hypotension, the change in SBP and the ST/heart rate index. The most powerful exercise variables were ΔPRP, followed by METs and exercise-induced arrhythmias. For the combined model, the top clinical and exercise variables were entered to arrive at the final model consisting of ΔPRP, age, METs, and ECG left ventricular hypertrophy, which were significant and in that order.

Figure 1



Kaplan-Meier survival curves for age, METs, and ECG left ventricular hypertrophy *(LVH)*.

Figure 2



Kaplan-Meier survival curves for ΔPRP.

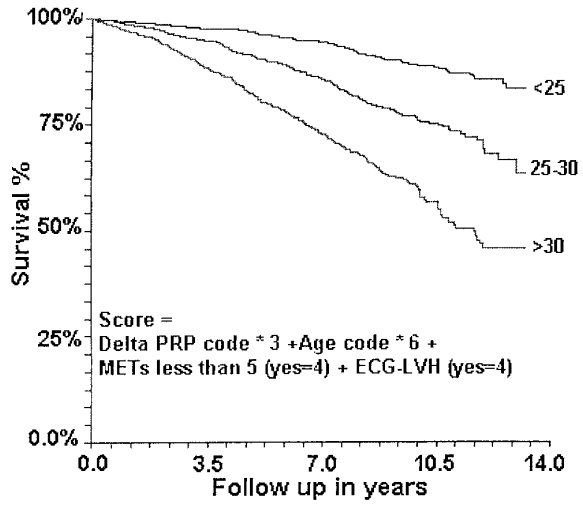
Notably, exercise-induced ECG abnormalities were not chosen as associated with time until death.

To simplify the score, these variables were coded or dichotomized as follows. Exercise capacity (METs) was dichotomized with use of a cut point of 5. ΔPRP was coded as $<10 \times 10^3 = 4$, $10\text{-}15 \times 10^3 = 3$, $15\text{-}20 \times 10^3 = 2$, and $>20 \times 10^3 = 1$. Age was coded as less than 30 years = 1, 30 to 45 years = 2, 45 to 65 years = 3, and greater than 65 years = 4. To give the coefficients the same weight, METs <5 and ECG left ventricular hypertrophy were coded as 0 for no and 4 for yes. "Good" responses were coded by use of small values and bad responses were coded by higher values. When only these 4 variables were entered in the model, the coefficients from the Cox model were 0.31, 0.61, 0.11, and 0.14, respectively, enabling construction of the following score: (coded ΔPRP · 3 + coded age · 6 + METs < 5 [4 = yes, 0 = no] + LVH on ECG [4 = yes, 0 = no]) as shown in Table IV.

ΔPRP code · 3 + age code · 6 + METs <5 (yes = 4) + ECG left ventricular hypertrophy (yes = 4)

The population was then coded according to the score, which ranged from 9 to 40. A score of less than 25 = 1, 25 to 30 = 2, and a score greater than 30 = 3. Univariate survival statistics were performed with Kaplan-Meier survival curves for the scores. The hazard ratios, confidence intervals, and *P* values for score values are shown in Table V and the Kaplan-Meier survival curves are shown in Figure 3. The score enabled the identification of a low risk group (46% of the cohort) with an

Figure 3



Kaplan-Meier survival curves for score. *LVH,* Left ventricular hypertrophy.

annual mortality rate of less than 1%, an intermediate risk group (29% of the cohort) with an annual mortality rate of about 2%, and a high-risk group (24% of the cohort) with an average annual mortality of about 4%.

Discussion

Background

Exercise testing is widely used clinically, and its many applications are the subject of a number of national[16,17] and international guidelines.[18,19] All the guidelines relative to ischemic heart disease recommend the standard exercise test as the first choice for the evaluation of the patient who has chest pain and does not have resting ECG abnormalities that affect the interpretation of the exercise ECG response.[1,2] Multicenter studies have presented treadmill results from large samples of patients. However, the patients are highly selected to fit the study protocol (Coronary Artery Surgical Study [CASS],[20] Quantitative Exercise Testing and Angiography [QUEXTA] study[21]), and series from institutions (Duke,[22] Mayo,[23] and Cleveland Clinics[24]) consist of target populations to answer specific research questions. Other large databases of treadmill tests with follow-up consist of asymptomatic individuals (US Air Force,[25] Cooper Clinic,[26] Israeli Air Force[27]) rather than clinical patients. Analysis of a large, consecutive population referred for diagnosis also provides an opportunity to compare our indications and methods to exercise laboratories throughout the Veterans Affairs Medical System. The latter is possible because we have assessed the behavior of Veterans Administration exercise laboratories by use of questionnaires.[28,29]

Table IV. Results of Cox hazard model selection considering the clinical and exercise test variables selected when grouped

Variable added	Z value	Probability level	χ^2
ΔPRP coded	11.79	<.001	137
Age coded	8.88	<.001	223
METs <5	4.12	<.001	242
ECG left ventricular hypertrophy	3.73	<.001	254

Table V. Values for the score and how the values perform prognostically

	Total (n = 3974) (%)	Hazard ratio	95% Confidence limit	Mortality rate (%)	
				5 y	10 y
Low risk (<25)	1824 (46%)			4	12
Intermediate risk (25-30)	1164 (29%)	2.3	2.3-2.4	10	25
High risk (>30)	935 (24%)	4.0	3.8-4.3	19	41

ΔPRP code · 3 + age code · 6 + METs <5 (yes = 4) + ECG left ventricular hypertrophy (yes = 4). Score of less than 25 = 1 (low risk), 25 to 30 = 2 (intermediate risk), and greater than 30 = 3 (high risk).

The strengths of this study include an unusually long follow-up, the inclusion of all consecutive clinical diagnostic referrals to 2 similar academically aligned Veterans Administration medical centers, and the application of standardized methods. Comparing the results with the results of our previous surveys provides a mirror to exercise testing Veterans Administration wide but expands the data by providing a careful count of responses. This study is one of many to document the safety of "symptom-and-sign" limited maximal exercise testing. One caveat must be considered, however: trained physicians or nurses were always in direct attendance of the test and the senior authors were always available for consultation.

Guidelines

Our clinical indications for the test were consistent with the American College of Cardiology/American Heart Association guidelines[17] and were similar to those of exercise laboratories throughout the Veterans Affairs system.[28] However, a great deal of variation existed at other centers in terms of criteria for abnormal results and whether physician presence is required during testing. We used the same ST-segment response criteria but only 28% of respondents to our survey used some type of treadmill score such as the Duke treadmill score.

Comparison with prior studies

Our study provides additional data regarding the prevalence of a wide range of exercise test responses and their prognostic impact. Notably, this represents the findings

Table VI. Prevalence of major exercise test responses from the available follow-up studies for comparison with our study

Variable	No. of studies	Mean	Our study
Age (mean y)	8	50	58
Exercise responses			
ST depression	8	50%	19%
ST elevation	7	3.5%	1.2%
VT	3	1%	1.1%
Frequent PVCs	8	11.6%	5.5%
LBBB	3	0.8%	0.4%
Maximum heart rate	9	134 beats/min	141 beats/min
METs	8	6.5	8.9
Maximum SBP	8	167 mm Hg	182 mm Hg
Exercise-induced hypotension	5	4.6%	2.5%
Annual mortality rate			
Cardiovascular	5	1.7%/y	NA
All-cause	5	2.2%/y	1.8%

Table VII. Frequency of clinical and exercise test variables chosen as significantly and independently associated with time until death in 9 previous prognostic studies

Variable	Out of 9 studies
Clinical	
Age*	2
Congestive heart failure	2
Myocardial infarction by history or Q waves	1
Resting ST depression*	1
Exercise responses	
Exercise capacity (METs)*	7
Angina	5
ST depression	4
Maximal heart rate	3
Maximal SBP	2
ST elevation	1
PVCs	1
Maximal double product*	1

*Variables chosen in our study (left ventricular hypertrophy includes ST depression).

among all consecutive patients referred for diagnosis rather than a selected group or a research population. Table VI provides a comparison with prior studies in regard to the frequency of the reported exercise test responses and mortality. The higher mean prevalence of abnormal responses and lower hemodynamic measurements in prior studies is because the other studies required cardiac catheterization, thus selecting a sicker population. This is in spite of the greater mean age in our population (58 vs 50 years). The rates of abnormal responses, including ventricular tachycardia, ST elevation, and exertional hypotension emphasize the need for proper training and prioritization of issues for certification of individuals performing exercise testing.[30]

Although many variables are univariately associated with risk for death, only 4 variables were independently and statistically associated with time to death. Table VII lists the number of times the major prognostic variables were chosen as significantly and independently predictive of time to death out of the times they were considered in the published prognostic studies.[31-39] The 4 chosen prognostic variables in the current study (age, METs, ΔPRP, and ECG left ventricular hypertrophy) are represented in this tabulation.

Other exercise variables not chosen in the final multivariate model but found to be univariately significant included maximum heart rate, exercise-induced ST depression, angina as the reason for stopping the test, arrhythmias during exercise, and exercise-induced RBBB. Exercise-induced hypotension was not significantly different between survivors and nonsurvivors, but the importance of SBP was reflected in the double product and the higher prevalence of failure to reach a SBP greater than 130 mm Hg in those who died. The failure of ventricular tachycardia to be independently predictive is consistent with our previous study.[40]

PRP

Myocardial oxygen uptake (Mvo_2) is an indicator of the ability of the coronary circulation to respond to myocardial metabolic demand. Although a direct measure of Mvo_2 is technically difficult, it can be estimated during exercise testing by the product of SBP and heart rate, generally called pressure rate product (PRP) or double product.[41,42] To take into account the change from rest, the PRP change from rest to maximal exercise (ΔPRP) can be calculated. Because both PRP and ΔPRP were shown to be reliable prognostic indicators, in previous studies we considered these measurements.

Saunamäki and Anderson[43,44] investigated the prognostic significance of ΔPRP in patients who performed a maximal exercise test in the third week after a myocardial infarction. Taking age and sex into account, they empirically found values of ΔPRP ranging between 1500 and 2500 (a value <2500 for patients <60 years old, <2000 for patients between 60 and 70 years old, and <1500 for patients >70 years old) to be predictive of death. Madsen and Gilpin[45] reported that the ΔPRP (<1500) was predictive of a reduced probability of survival after 5 years (59% vs 74%) in a similar group of post–myocardial infarction patients. This finding was confirmed in the thrombolysis era patients of the Gruppo Italiano por lo Studio della Sopravvivenza nell'Infarto Miocardioco-2 (GISSI-2) study.[46] The only prior study to consider and find PRP significantly associated with time to death in non-MI patients (as indicted in Table VII) was from the Seattle Veterans Administration.[47] In a previous study of exercise testing in a large sample of apparently healthy subjects, peak exercise systolic and diastolic, as well as Δsystolic blood pressure were found to increase with advancing age.[48]

Ischemic variables

The relative unimportance of the ischemic variables may be due to our inability to censor on interventions for ischemia (ie, removal of patients who received surgical or catheter interventions from observation when the intervention occurs during follow-up) and the consideration of all-cause mortality instead of cardiovascular mortality. This may also explain why the ischemic variables included in the Duke score[22] did not predict all-cause mortality. Although all-cause mortality has advantages over cardiovascular mortality as an end point,[49] the Duke score was developed with use of the end points of infarction and cardiovascular death.[32] In addition, interventions such as bypass surgery or catheter procedures were censored in the Duke study (that is, subjects were removed from the survival analysis when interventions occurred). Such censoring should increase the association of ischemic variables with outcome by removing patients whose disease has been alleviated and thereby would not be as likely to experience the outcome. We did not censor patients on the basis of whether they had a cardiovascular procedure during follow-up because we do not have that information. From a previous study with a Veterans Administration patient population that was not selected for cardiac catheterization with an annual all-cause mortality of 2.8%, we found that 60% of deaths were cardiovascular and that 3% of patients were censored in follow-up because of bypass surgery.[50] The contradictory results could also be due to the more effective methods of treatment currently available for coronary disease.

The use of interventions as end points falsely strengthens the association of ischemic variables with end points because the ischemic responses clinically result in the intervention being performed. Although some investigators have justified their use by requiring a time period to expire after the test before using the intervention/procedure as an end point, this still influences the associations between test responses and end points. Another problem has been that variables predicting infarction can be different than those predicting death.

If the aim is to predict infarct-free survival, the Duke treadmill score is preferred to our score because the Duke investigators censored and predicted infarct-free survival. Thus the Duke treadmill score can be used to decide which patients should get interventions. If diagnosis is the issue, either the Duke score or other treadmill diagnostic scores are indicated.[51,52]

Summary

This study of a large number of consecutive patients referred for diagnostic exercise testing at 2 Veterans Administration medical centers provides rates of abnormal responses that can be expected in clinical exercise laboratories. The study has demonstrated the prognostic power of 4 simple pieces of information: ΔPRP, exercise capacity, age, and ECG left ventricular hypertrophy. These variables can be used in a simple additive score to powerfully stratify the expected risk in a population that receives modern medical treatment.

Although ischemic ECG variables and other hemodynamic variables were univariately associated with death, they were not chosen in the hazard model as independently and significantly predictive of time until death. It may well be that modern therapies for these responses and the associated conditions are so good that they are not chosen in the hazard model. Although these data are unique in terms of the size of the sample and consistency of method, the major limitations of only having all-cause mortality, no data on myocardial infarction as an end point nor interventional procedures for censoring and the lack of women are apparent. However, we have presented the responses to testing in a large series of consecutive male patients referred for exercise testing for diagnosis of possible heart disease, all tested according to consistent and standardized methods.

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