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

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Objectives. **We sought to determine the relative influence of estimated functional capacity and thallium-201 (Tl-201) single-photon emission computed tomographic (SPECT) findings on prediction of short-term all-cause and cardiac-related mortality.**

Background. **Decreased functional capacity and abnormal Tl-201 SPECT findings are predictive of increased cardiovascular risk and mortality. However, the relative importance of these variables as predictors of all-cause mortality is not well established.**

Methods. **Analyses were based on 3,400 consecutive adults undergoing symptom-limited exercise Tl-201 SPECT testing at the Cleveland Clinic Foundation between September 1990 and December 1993; none had previous invasive procedures, heart failure or valve disease. Estimated functional capacity, classified by age and gender, and thallium perfusion defects, expressed as a stress extent thallium score on a 12-segment scale, were analyzed to determine their relative prognostic importance during 2 years of follow-up.**

Results. **Of 3,400 patients, 108 (3.2%) died during follow-up; 32 deaths were identified as cardiac related. On univariable analysis, estimated functional capacity was a strong predictor of death, with 62 (57%) deaths occurring in patients achieving <6 metabolic equivalents (METs) (log-rank chi-square 86, $p < 0.0001$). On multivariable analysis, the strongest independent predictors of all-cause mortality were fair or poor functional capacity (adjusted relative risk [RR] 3.96, 95% confidence interval [CI] 2.36 to 6.64, chi-square 27, $p < 0.0001$) and age (adjusted RR for 10 years 2.25, 95% CI 1.80 to 2.80, chi-square 27, $p < 0.0001$). The presence of SPECT thallium perfusion defects was a less powerful predictor of death (for each two additional segments with defects, adjusted RR 1.21, 95% CI 1.03 to 1.43, chi-square 5, $p = 0.02$). Cardiac mortality was predicted by both fair or poor functional capacity (adjusted RR 4.37, 95% CI 1.59 to 12.00, chi-square 8, $p = 0.004$) and by stress extent thallium score (adjusted RR 1.62, 95% CI 1.25 to 2.11, chi-square 13, $p = 0.0003$).**

Conclusions. **In this clinically low risk group, estimated functional capacity was a strong and overwhelmingly important independent predictor of all-cause mortality among patients undergoing exercise Tl-201 SPECT testing. The extent of myocardial perfusion defects was of comparable importance for the prediction of cardiac mortality.**

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The importance of functional capacity as a predictor of cardiovascular risk is well established among healthy adults (1–4), patients referred for exercise electrocardiographic (ECG) treadmill testing (5–10) and patients who have undergone coronary angiography (11–13). Abnormalities on exercise thallium-201 (Tl-201) scintigrams are predictive of increased cardiovascular risk (14,15), and the presence and extent of perfusion abnormalities have been shown (16,17) to add incremental prognostic value to the findings of clinical and exercise data.

Previous studies of functional testing and risk have been criticized for not focusing on all-cause mortality, which is a "hard," unambiguous end point, instead of, or in addition to, combined fatal and nonfatal cardiac end points (18,19). The relative importance of thallium results and functional capacity as independent predictors of all-cause mortality has not been well defined. Therefore, the objective of this study was to determine the importance of functional capacity, as estimated in routine clinical practice, as a predictor of all-cause and cardiac mortality among patients referred for symptom-limited exercise thallium testing.

Methods

Study group. The subjects for this investigation were consecutive adults undergoing symptom-limited exercise treadmill thallium testing at the Cleveland Clinic Foundation between

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Abbreviations and Acronyms

CI = confidence interval
df = degrees of freedom
ECG = electrocardiogram, electrocardiographic
METs = metabolic equivalents
OR = odds ratio
RR = relative risk
SPECT = single-photon emission computed tomography (tomographic)
Tl-201 = thallium-201

September 1990 and December 1993. All patients were undergoing their first treadmill test at the Cleveland Clinic Foundation. Methods of prospective data acquisition have been described in detail elsewhere (20). Exclusion criteria included any history of coronary angiography or invasive procedures, previous cardiac surgery, congestive heart failure, valvular heart disease, pre-excitation syndrome and congenital heart disease. All patients gave written, informed consent before undergoing exercise treadmill testing.

Clinical data. Before each treadmill test, a structured interview and chart review yielded data on symptoms, medications, coronary risk factors, previous cardiac events and number of cardiac and noncardiac diagnoses (21,22). *Rest hypertension* was defined as a rest systolic blood pressure ≥140 mm Hg or a rest diastolic blood pressure ≥90 mm Hg or treatment with antihypertensive medications (23). *Assessment of diabetes* was based on chart review, questioning and medication use. *Lipid-related analyses* primarily focused on use of lipid-lowering drugs because many patients did not have lipid profiles at the time of testing.

Exercise testing. Treadmill testing was carried out according to standard protocols, usually Bruce and modified Bruce (24). Although nitrates were explicitly discouraged on the day of the test, there was no laboratory policy regarding management of beta-adrenergic blocking agents; this was left to the discretion of the referring physicians. To facilitate estimation of exercise capacity, the patients were not allowed to lean on handrails during exercise. During each stage of exercise, data on symptoms, rhythm, heart rate, blood pressure (by indirect arm-cuff sphygmomanometry), estimated work load in metabolic equivalents (METs) and ST segments were collected and entered on-line. Estimated functional capacity in METs was estimated from standard published tables based on protocol and total time completed in the final stage (22); a MET is a measure of oxygen consumption equal to 3.5 ml/kg per min, which represents basal, rest metabolic needs. Estimated functional capacity was also evaluated against the aerobic capacity classification (25) on the basis of age and gender from average maximal oxygen consumption values of physically active and sedentary men and women in the United States and abroad (Table 1). Subjects were also asked to provide a rating of perceived exertion during each stage of exercise on a 1 to 10 modified Borg scale (26). ST segments were analyzed as a binary variable using all leads except a VR; an *ischemic response* was considered present if there was ≥1 mm of horizontal or downsloping ST segment depression 80 ms after the J point, or if there was ≥1 mm of additional ST segment elevation in leads without pathologic Q waves.

Thallium scintigraphy. Patients received an injection of 2 to 3 mCi of Tl-201 1 min before termination of the treadmill test. SPECT imaging using a standard acquisition methodology (27) was performed within 10 min of stress and repeated 3 to 4 h later for redistribution imaging. Images were reconstructed using a Hamming filter and were projected in short-axis, vertical and horizontal long-axis views in a side by side display. Ischemia was interpreted in the presence of >20% reversibility and scar by the presence of counts <80% of maximum (<70% for the posterior wall) (27). The coding of the thallium data was done in a blinded manner with regard to clinical and exercise data.

Thallium scans were coded according to a 12-segment system as follows: anterior, anterolateral, anteroseptal, apical and septal walls corresponding to the left anterior descending coronary artery distribution; inferior, inferoseptal and posteroseptal walls corresponding to the right coronary artery distribution; and lateral, inferolateral, posterolateral and posterior walls corresponding to the left circumflex artery distribution. Analyses of the impact of thallium abnormalities on mortality were primarily based on the total number of abnormal segments, irrespective of whether perfusion defects were fixed or reversible; this was termed the *stress extent thallium score*.

End points. The primary end point of this study was all-cause mortality during ~2 years of follow-up. *Mortality* was ascertained using the Social Security Death Master Files (Epidemiology Resources), a source of death statistics that is slightly less accurate but more current and specific than the National Death Index (28,29). The *cause of death* was assessed by examination of death certificates, and cardiac mortality was considered a secondary end point; probable causes of death

Table 1. Classification of Estimated Functional Capacity According to Age and Gender

Age (yr)	Estimated Functional Capacity (METs) Poor	Fair	Average	Good	High
Women					
≤29	<7.5	8–10	10–13	13–16	>16
30–39	<7	7–9	9–11	11–15	>15
40–49	<6	6–8	8–10	10–14	>14
50–59	<5	5–7	7–9	9–13	>13
≥60	<4.5	4.5–6	6–8	8–11.5	>11.5
Men					
≤29	<8	8–11	11–14	14–17	>17
30–39	<7.5	7.5–10	10–12.5	12.5–16	>16
40–49	<7	7–8.5	8.5–11.5	11.5–15	>15
50–59	<6	6–8	8–11	11–14	>14
≥60	<5.5	5.5–7	7–9.5	9.5–13	>13

METs = metabolic equivalents (1 MET = 3.5 ml/kg per min of oxygen consumption).

Table 2. Baseline Characteristics According to Gender

Characteristic	Men (n = 2,139)	Women (n = 1,261)
Age (yr)	58.1 ± 12.0	58.6 ± 12.1
SBP (mm Hg)	137 ± 19	134 ± 21
DBP (mm Hg)	88 ± 11	85 ± 11
Hypertension	885 (41%)	564 (45%)
Hypertension treatment	778 (36%)	505 (40%)
Current smoker	378 (18%)	188 (15%)
Beta-blocker	260 (12%)	185 (15%)
Calcium blocker	440 (21%)	286 (23%)
Lipid medication	181 (8%)	84 (7%)
Diabetes	294 (14%)	145 (12%)
Chest pain	893 (42%)	863 (69%)
Exertional dyspnea	388 (18%)	417 (33%)
Palpitations	271 (13%)	355 (28%)
Prior coronary event	271 (13%)	70 (5%)

Data presented are mean value ± SD or number (%) of patients. DBP = diastolic blood pressure; SBP = systolic blood pressure.

were coded by a reviewer who had no knowledge of the clinical, exercise and thallium data.

Statistical analyses. Subjects were classified as having high, good, average, fair or poor estimated functional capacity on the basis of age- and gender-specific criteria in Table 1 (25). The associations of gender and thallium abnormalities with age- and gender-specific estimated functional capacity classification were tested according to the Mantel extension test for trend (30).

The associations of estimated functional capacity, summed stress thallium score and all-cause mortality were initially analyzed using Kaplan-Meier plots. Differences between survival curves were compared using the log-rank chi-square statistic.

Multivariables Cox proportional hazards analyses were performed to assess the impact of estimated functional capacity on all-cause mortality after adjusting for potential confounders. Four sequential models were analyzed, mimicking the presentation of data in clinical practice. The first model incorporated pretest clinical variables, including age, gender, previous coronary events, cardiovascular medications and standard cardiovascular risk factors. The next model added estimated functional capacity, either as a continuous variable (estimated METs) or as a categoric variable (fair or poor functional capacity vs. average, good or high, as classified in Table 1). The third model added other exercise variables, including percent age-predicted maximal heart rate achieved, increase in systolic blood pressure, test-terminating angina and exercise-induced ventricular tachycardia. The final model added the stress extent thallium score.

Supplementary analyses were performed 1) to test for age- or gender-related interactions, or both, on the association between estimated functional capacity and all-cause mortality using interaction terms; and 2) to only consider events occurring at least 6 months after testing, to reduce potential confounding caused by procedure-related deaths. Analyses of cardiac mortality were adjusted for only three covariates (age, gender and stress extent thallium score) to avoid model overfitting given the relatively small number of events (n = 32). All analyses were performed using the SAS 6.08 statistical package (31).

Results

Baseline and exercise characteristics. The baseline clinical characteristics of the 2,139 men and 1,261 women analyzed are summarized in Table 2, and their exercise characteristics are summarized in Table 3. The most common reasons cited for testing were "rule out coronary artery disease" (84%), "follow up coronary artery disease" (9%), "preoperative evaluation" (3%) and "multiple coronary risk factors" (1%). The most common reason for test termination was fatigue (1,976 men [92%], 1,206 women [96%]). Women were more likely to have test-terminating angina (75 men [3.5%], 73 women [5.9%]) but were less likely to have test-terminating ST segment changes (81 men [3.8%], 20 women [1.6%]). According to the age- and gender-specific classifications in Table 1, 36% of men and 48% of women had poor or fair estimated functional capacity.

Abnormal thallium scan results were noted in 623 men (29%) and 94 women (7%). One or more reversible thallium defects were present in 309 men (14%) and 55 women (4%). The distribution of stress extent thallium score is summarized in Table 3.

As noted in Table 3, among both men and women, the proportion of ischemic scans increased as estimated functional

Table 3. Exercise Characteristics According to Gender

Characteristic	Men	Women
Protocol		
Bruce	1,058 (49%)	172 (14%)
Modified Bruce	768 (36%)	755 (60%)
CAEP	92 (4%)	133 (10%)
Other	221 (11%)	201 (16%)
Est peak METs	8.7 ± 2.5	6.8 ± 1.9
Peak HR (beats/min)	153 ± 23	151 ± 21
Peak SBP (mm Hg)	196 ± 28	184 ± 28
Ischemic ST seg changes*	382 (23%)	153 (16%)
VT	23 (1%)	2 (<1%)
Anginal chest pain	219 (10%)	245 (19%)
Failure to reach 85% of target HR	320 (15%)	18 (14%)
Hypotensive response	50 (2%)	27 (2%)
Normal Tl scan	1,516 (71%)	1,167 (93%)
Stress extent Tl score		
1–2	278 (13%)	50 (4%)
3–4	173 (8%)	26 (2%)
>4	172 (8%)	18 (1%)
Ischemia w/good ex capacity	43/417 (10%)	7/343 (2%)
Ischemia w/poor ex capacity	62/290 (22%)	18/211 (9%)

*Of those subjects with interpretable ST segments (1,690 men, 957 women). Data presented are mean value ± SD or number (%) of patients. CAEP = chronotropic assessment exercise protocol; Est = estimated; Ex = exercise; HR = heart rate; seg = segment; Tl = thallium; w/ = with; other abbreviations as in Tables 1 and 2.

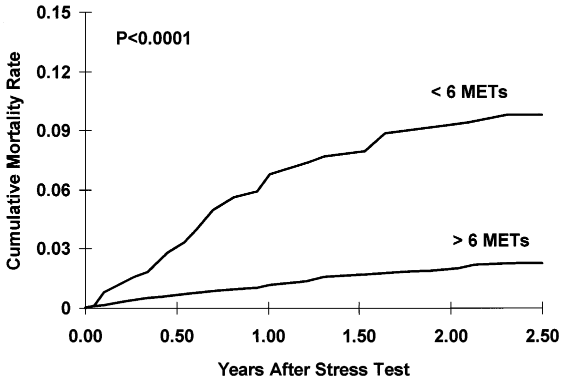


Figure 1. Kaplan-Meier plot of all-cause mortality as a function of ability to achieve 6 METs of estimated work during symptom-limited exercise.

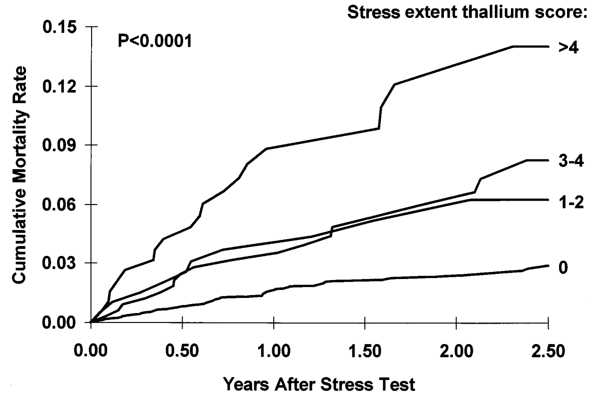


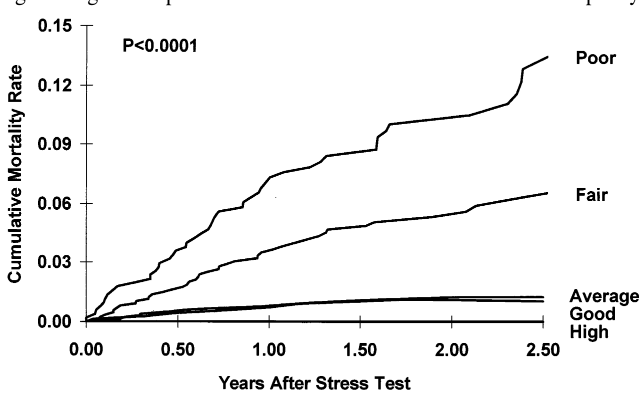
Figure 3. Kaplan-Meier plot of all-cause mortality as a function of stress extent thallium score.

capacity worsened (Mantel extension test for trend, in men: chi-square 26 with 1 degree of freedom [df], $p < 0.0001$; in women: chi-square 12 with 1 df, $p = 0.0006$).

Prediction of all-cause mortality. During ~2 years of follow-up, there were 83 deaths among men (4%) and 25 deaths among women (2%). When classified according to the ability to achieve 6 METs of work (Fig. 1), patients with impaired estimated functional capacity had a markedly higher all-cause mortality rate (log-rank chi-square 86 with 1 df, $p < 0.0001$); of note, 57% of the deaths occurred among patients who did not achieve 6 METs. When classified according to age- and gender-specific functional capacity categories (Fig. 2), patients with fair or poor functional capacity had markedly higher all-cause mortality rates (log-rank chi-square 105 with 4 df, $p < 0.0001$); 81% of the deaths occurred among those with fair or poor functional capacity. All subjects with good, average and high functional capacity classifications had very low mortality rates.

The stress extent thallium score was also predictive of all-cause mortality (Fig. 3), with 2-year cumulative mortality rates ranging from ~2% in subjects with normal thallium scans to >12% in those with at least five abnormal segments (log-rank chi-square 33 with 3 df, $p < 0.0001$).

Figure 2. Kaplan-Meier plot of all-cause mortality as a function of age- and gender-specific classification of estimated functional capacity.



Multivariable analyses. Results of sequential proportional hazards analyses are summarized in Figure 4 and Table 4. Adding estimated functional capacity to pretest clinical variables markedly improved prediction of death, with a lesser degree of improvement for stress extent thallium score. After adjusting for age, gender, risk factors, medication use, stress extent thallium score (presence of thallium ischemia) and other exercise test variables, functional capacity remained a powerful and independent predictor of all-cause mortality. No significant age- or gender-related interactions were noted, which modified the association between worse functional capacity and all-cause mortality.

If an abnormal test result prompts performance of risk-associated procedures, such as coronary angiography, coronary angioplasty and coronary artery bypass grafting, any apparent association between the test result and all-cause mortality may be biased by the adverse outcomes related to those procedures or actions taken as a result of them. Therefore, we analyzed supplementary multivariable Cox models in which subjects who died and had undergone coronary angiography within 6 months of the exercise test were excluded. In these analyses there were 98 deaths. Estimated functional capacity remained

Figure 4. Impact of clinical, functional capacity (Func Cap) exercise (Ex Vars) and thallium (Thal Score) variables on prediction of all-cause mortality: results of sequential proportional hazards analyses.

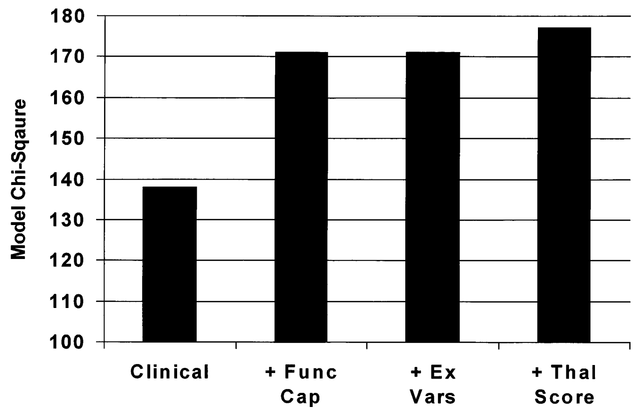


Table 4. Results of Proportional Hazards Analyses for Prediction of All-Cause Mortality: Final Models

Variable	RR (95% CI)	Chi-Square	Value
Estimated Functional Capacity as Continuous Variable			
Age (10 yr)	1.92 (1.51–2.45)	28	<0.0001
Gender (female)	0.37 (0.22–0.59)	17	<0.0001
Peak METs (−2 METs)	1.88 (1.52–2.33)	34	<0.0001
Stress extent Tl score (+2 units in score)	1.20 (1.01–1.41)	5	0.03
Estimated Functional Capacity as Categoric Variable			
Age (10 yr)	2.25 (1.80–2.80)	27	<0.0001
Gender (female)	0.49 (0.31–0.78)	9	<0.003
Poor or fair functional capacity	3.96 (2.36–6.64)	27	<0.0001
Stress extent Tl score (+2 units in score)	1.21 (1.03–1.43)	5	0.02

See text for details of model building. CI = confidence interval; RR = relative risk; other abbreviations as in Tables 1 and 3.

a powerful independent predictor of all-cause mortality; having a fair or poor age- and gender-specific functional capacity was associated with an adjusted hazard ratio of 4.03 (95% confidence interval [CI] 2.35 to 6.82, $p < 0.0001$).

Prediction of cardiac mortality. During follow-up, 27 men (1.3%) and 7 women (0.6%) died of cardiac causes. Patients who died of noncardiac causes did not have higher prevalences of chronic lung disease ($p > 0.05$) or diabetes ($p > 0.7$) and had a marginally lower prevalence of peripheral vascular disease (11% vs. 25%, $p = 0.07$). When classified according to the ability to achieve 6 METs of work, patients with impaired exercise capacity had a markedly higher cardiac mortality rate during follow-up (log-rank chi-square 28 with 1 df, $p < 0.0001$); of note, 59% of the cardiac deaths occurred among patients who did not achieve 6 METs. When classified according to age- and gender-specific physical fitness category, patients with fair or poor estimated functional capacity had markedly higher all-cause mortality rate (log-rank chi-square 34 with 4 df, $p < 0.0001$); 84% of the deaths occurred among those with fair or poor physical fitness classifications. Subjects with good, average and high physical fitness classifications had very low cardiac mortality rates. Thus, the predictive value of failure to achieve 6 METs is better for identifying high risk patients when advanced age and male gender are included in the assessment.

After adjusting for age, gender and stress extent thallium score, cardiac mortality was predicted by both fair or poor functional capacity (adjusted relative risk [RR] 4.37, 95% CI 1.59 to 12.00, chi-square 8, $p = 0.004$) and by stress extent thallium score (for each increment of two segments, adjusted RR 1.62, 95% CI 1.25 to 2.11, chi-square 13, $p = 0.0003$). Results of sequential proportional hazards analyses are shown in Figure 5; stress extent thallium score contributed more to the model's chi-square than did functional capacity as estimated in METs.

On univariate analyses, ST segment changes in those patients who had interpretable ECGs at baseline were not predictive of all-cause mortality but tended to predict cardiac mortality (odds ratio [OR] 2.07, 95% CI 0.89 to 4.88, $p = 0.09$). Marked ST segment changes, defined as at least 2 mm of horizontal or downsloping ST segment depression, was not predictive of all-cause or cardiac mortality.

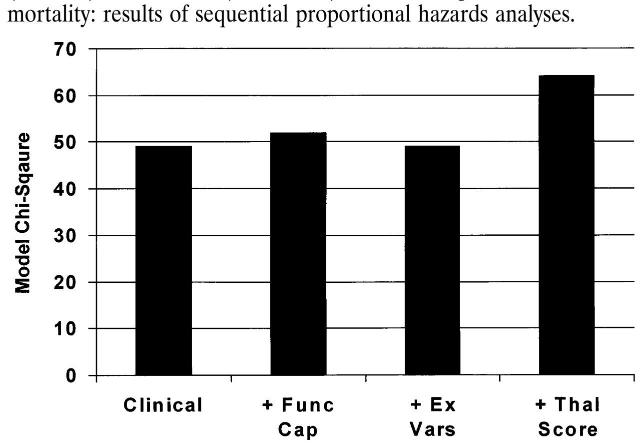
Post-test coronary angiography and revascularization. During follow-up, 398 subjects underwent coronary angiography and 70 underwent percutaneous or surgical revascularization. After adjusting for age and gender, thallium ischemia was a very strong predictor of subsequent coronary angiography (for each additional abnormal segment: OR 1.58, chi-square 264, $p < 0.0001$), whereas functional capacity was only moderately predictive (for 1 MET increase: OR 0.93, chi-square 6, $p = 0.01$). Similarly, thallium ischemia was predictive of revascularization (OR 1.32, chi-square 34, $p < 0.0001$), whereas functional capacity was not predictive (OR 0.97, chi-square 0.2, $p > 0.6$).

Discussion

In a group of 3,400 adults undergoing exercise thallium testing for evaluation of known or suspected coronary artery disease, impaired estimated functional capacity was strongly related to death from all causes during 2 years of follow-up. Impaired functional capacity was also correlated with a greater likelihood of thallium perfusion abnormalities, which themselves were also predictive of all-cause mortality. On multivariable analyses, functional capacity remained a very strong, independent predictor of all-cause mortality, whereas stress extent thallium score was less predictive. Estimated functional capacity and stress extent thallium score were both equally predictive of cardiac mortality.

The overriding importance of the association between estimated functional capacity and all-cause mortality is especially noteworthy in that the majority of the deaths (86 of 108) occurred in patients with impaired (either fair or poor) functional capacity. This is in contrast to many risk factors, which, although they may identify certain high risk subsets, are nonetheless associated with a minority of actual events (32).

Figure 5. Impact of clinical, functional capacity (Func Cap) exercise (Ex Vars) and thallium (Thal Score) variables on prediction of cardiac mortality: results of sequential proportional hazards analyses.



Functional capacity and cardiac mortality. Podrid et al. (6) noted increased mortality in patients achieving <6 METs, whereas McNeer et al. (11) and Weiner et al. (12) found 5 METs and 2 METs, respectively, predictive of poor prognosis and increased prevalence of three-vessel or left main coronary artery disease. Similarly, Dagenais et al. (9) and McNeer et al. (11) found that patients with ≥10 METs and 13 METs functional capacity, respectively, had 100% survival at follow-up. Weiner et al. (12) and other groups (1,33,34) have found an inverse relation between high physical fitness and cardiovascular mortality (1,33,34). Peak exercise capacity has been incorporated into prognostic scores, including the Duke treadmill exercise score (35), the Veterans Affairs Medical Center questionnaire score (36) and the multivariate exercise score (37).

Associations between fitness and all-cause mortality in healthy adults. Data from the Harvard Alumni Health Study (38,39) showed a significant decrease in mortality rates among those who remained physically active. Blair et al. (4) found a significant correlation in physical fitness and all-cause mortality for both men and women after adjusting for age and standard coronary artery disease risk factors.

Relative influence of functional capacity and perfusion imaging on mortality. Previous studies investigated the prognostic significance of clinical exercise and thallium-201 variables on mortality and future, nonfatal cardiac events. Machecourt et al. (40) found scintigraphic, but not exercise variables, to be predictive of total and cardiovascular mortality. Iskandrian et al. (16), Travin et al. (41) and Gill et al. (42) found exercise work load to be a significant predictor of cardiovascular mortality but did not assess total mortality. Several studies focused only on cardiovascular mortality and morbidity in their analysis, and functional capacity was not a statistically significant predictor of cardiovascular mortality (15,17,43,44). Other studies investigating the prognostic implications of thallium imaging that included total mortality and cardiovascular mortality (45,46) involved dipyridamole infusion or atrial pacing among patients presumed to have a very low functional capacity.

Influence of functional capacity on all-cause versus cardiac mortality. The current study extends the findings of previous investigations in several important respects. 1) It demonstrates that functional capacity, *as estimated in routine clinical practice*, is a strong and independent predictor of *all-cause* mortality, independent of thallium SPECT results. Patients exercised according to different protocols, *without sophisticated gas exchange techniques*, precluding the simple measurement of exercise time. Nonetheless, the estimated values of functional capacity were prognostically significant. 2) The current data identify both estimated functional capacity and stress extent thallium score to be independent predictors of mortality; the former stratified risk for both all-cause and cardiac mortality, whereas the latter was better at stratifying risk for cardiac mortality. 3) Failure to consider all-cause mortality is cited as a major criticism of some previous studies (18,19). When considering variables predictive of only cardiac mortality, noncardiac deaths need to be censored (47). In this regard, exercise capacity, as an independent predictor of both all-cause mortality and cardiovascular disease, combined with other clinical, exercise or angiographic information, becomes a very powerful tool. To our knowledge, this is the first study describing the association of exercise capacity, by age- and gender-specific classification, with all-cause mortality in a large cohort of patients undergoing treadmill thallium testing at a single center.

Clinical implications. Exercise thallium testing is often performed to aid the diagnosis, prognosis and functional evaluation of patients with known or suspected coronary artery disease. It has been suggested that radionuclide imaging provides little additional diagnostic or prognostic information for patients with severe coronary disease and normal rest ECGs (48).

Thallium scintigraphy is useful in patients with abnormal rest ECGs, in those with an intermediate probability of having disease and in defining prognosis of patients with known or suspected coronary artery disease, especially in those with previous myocardial infarction (49,50). The results of the current study suggest that clinicians should pay particular attention to functional capacity when assessing risk of all-cause death, whereas both functional capacity and thallium results should be considered when assessing risk of cardiac death.

Study limitations. Several limitations need to be considered. The group studied had relatively low risk, with low rates of cardiac death. The low overall death rates imply that although impaired exercise capacity is a sensitive predictor of mortality, the positive predictive value is low. Women had very low rates of abnormal thallium scans; some false negative results cannot be excluded. Patients were more likely to be referred for angiography and revascularization on the basis of abnormal scintigrams as opposed to decreased exercise capacity; this may partly explain why abnormal functional capacity was a better predictor of all-cause mortality than scintigraphic evidence of ischemia. The use of incremental protocols has been shown to overestimate exercise capacity (51); nonetheless, estimated functional capacity was strongly predictive of death. Thallium results were analyzed by a semiquantitative approach; it is possible that Tl-201 redistribution would have been a stronger variable by a fully quantitative analysis. Data on lung uptake were not available; this has been shown to be a powerful predictor of risk. Follow-up was relatively short term, just under 2 years. Whether functional capacity remains a strong predictor of all-cause and cardiac mortality in the long term in these patients needs to be further investigated. Longer term data would better clarify for physicians how much of a distinction, if any, needs to be made regarding prediction of all-cause, as opposed to strictly cardiac, mortality.

Conclusions. Among patients referred for exercise thallium testing for evaluation of suspected coronary disease, estimated functional capacity is a very powerful and independent predictor of both all-cause and cardiac mortality. The association between estimated functional capacity and risk of death meets accepted criteria for a valid epidemiologic relation. The association was strong, with a three- to fourfold increase in risk. There is a temporal sequence, as demonstrated by the Kaplan-Meier plots, as well as a "dose-response" relation: the worse the estimated functional capacity, the higher the risk for death. The association persisted after adjusting for potential confounders, especially the stress extent thallium score. The results are consistent with those of previous investigations of healthy subjects and patients undergoing exercise electrocardiography or coronary angiography. Finally, the association is biologically plausible.

It is unclear from our data whether functional status reflects a modifiable risk factor for mortality or a measure of physiologic deterioration that, like age, is not amenable to medical interventions. At least one meta-analysis has suggested that cardiac rehabilitation after myocardial infarction is associated with lower mortality (52). Further research will be needed to confirm the association between functional capacity and death and to determine how best to use this information in designing optimal diagnostic and therapeutic approaches for the patient being evaluated for possible coronary disease.

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