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Independent Contribution of Myocardial Perfusion Defects to Exercise Capacity and Heart Rate Recovery for Prediction of All-cause Mortality in Patients With Known or Suspected Coronary Heart Disease

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OBJECTIVES The goal of this study was to determine the value of thallium^{201} single photon emission computed tomography (SPECT) imaging for prediction of all-cause mortality when considered along with functional capacity and heart rate recovery.

BACKGROUND Myocardial perfusion defects identified by thallium^{201} SPECT imaging are predictive of cardiac events. Functional capacity and heart rate recovery are exercise measures that also have prognostic implications.

METHODS We followed 7,163 consecutive adults referred for symptom-limited exercise thallium SPECT (mean age 60 ± 10, 25% women) for 6.7 years. Using information theory, we identified a probable best model relating nuclear findings to outcome to calculate a prognostic nuclear score.

RESULTS There were 855 deaths. Intermediate- and high-risk prognostic nuclear scores were noted in 28% and 10% of patients. Compared with those with low-risk scans, patients with an intermediate-risk score were at increased risk for death (14% vs. 9%, hazard ratio: 1.67, 95% confidence interval [CI]: 1.44 to 1.95, $p < 0.0001$), while those with high-risk scores were at greater risk (24%, hazard ratio: 2.98, 95% CI: 2.49 to 3.56, $p < 0.0001$). In multivariable analyses that adjusted for clinical characteristics, functional capacity and heart rate recovery, an intermediate-risk nuclear score remained predictive of death (adjusted hazard ratio: 1.50, 95% CI: 1.28 to 1.76, $p < 0.0001$), as did a high-risk score (adjusted hazard ratio: 2.76, 95% CI: 2.13 to 2.56, $p < 0.0001$). Impaired functional capacity and decreased heart rate recovery provided additional prognostic information.

CONCLUSIONS Myocardial perfusion defects detected by thallium SPECT imaging are independently predictive of long-term all-cause death, even after accounting for exercise capacity, heart rate recovery and other potential confounders. (J Am Coll Cardiol 2001;37:1558–64) © 2001 by the American College of Cardiology

Myocardial perfusion imaging is used for diagnosing coronary artery disease and for risk stratification in patients with known or suspected disease (1–5). Although imaging results are often considered alongside results of exercise electrocardiography for prediction of cardiac events, recent studies have highlighted the ability of nonelectrocardiographic exercise measures, such as functional capacity (6,7) and heart rate recovery (8,9), to predict mortality. Relatively little is known about how to best integrate these exercise measures with nuclear perfusion abnormalities for optimal risk stratification. In this study, we sought to assess the independent long-term importance of thallium^{201} single photon emission computed tomography (SPECT) perfusion abnormalities relative to functional capacity and heart rate recovery for prediction of all-cause mortality in a large cohort of patients. All-cause mortality was studied as an objective and unbiased end point (10,11).

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METHODS

Patient sample. Consecutive adults (age ≥30 years) referred for thallium SPECT imaging in conjunction with symptom-limited exercise testing between September 1990 and December 1993 at the Cleveland Clinic Foundation were studied. Patients with known heart failure or left ventricular dysfunction (ejection fraction ≤40%), valvular disease and a history of pacemaker implantation were excluded. Because we used the Social Security Death Index (12) for assessing outcome, foreign nationals were also excluded. The study protocol was approved by the local institutional review board.

Clinical data. The methods used for prospective study of patients undergoing stress testing at our institution have been described in detail elsewhere (6,13). Since 1990, all patients undergoing stress testing undergo a structured interview and chart review. Data collected prospectively

Abbreviations and Acronyms

CI = confidence interval
METs = metabolic equivalents
SPECT = single photon emission computed tomography

include existing medical diagnoses, symptoms, risk factors, medications and prior procedures. All data are entered on-line before exercise testing; thus, clinical data collected are not influenced by stress or nuclear study results.

Exercise testing, functional capacity and heart rate recovery. The methods of exercise testing and prospective, computerized data collection used in our laboratory have been described in detail elsewhere (13,14). Estimated functional capacity in metabolic equivalents (METS) was classified as high, good, average, fair or poor for age and gender based on a classification system (6) that has been validated. Patients were unfit if their age- and gender-based functional capacity was fair or poor. Heart rate recovery was defined as the difference between heart rate at peak exercise and 1 min into a recovery cool-down period; a value of ≤12 beats/min was abnormal (8). We chose not to study chronotropic response to exercise (13,15) because patients taking beta-adrenergic blocking agents were not excluded. We did not analyze ST-segment responses or Duke treadmill scores (16,17) because of the presence of factors such as digoxin use or marked baseline electrocardiographic abnormalities that would limit their interpretation.

Thallium^{201} SPECT imaging. We have published scintigraphic methods used in our laboratory in the early 1990s (18,19). The heart was divided into twelve segments and, to avoid any inherent prognostic limitation related to a 12-segment model (20), each segment was weighted according to its relative contribution to total left ventricular mass: anterior (weighted by 3 mU), anterior-lateral (3 mU), anterior-septal (3 mU), septal (2 mU), apical (1 mU), inferior (2 mU), inferior-lateral (2 mU), inferior-septal (2 mU), lateral (3 mU), posterior (1 mU), posterior-lateral (1 mU) and posterior-septal (1 mU). Each segment was coded as normal, fixed (scar) or reversible (ischemia). The justification for mass weightings has been reported (20). In cases of suspected artifact or attenuation, the segment was considered normal.

As previously described (18), images were displayed and interpreted using quantitative color scales. Myocardial counts were referenced to peak myocardial activity on the resting images; thus, counts were expressed as a percent of maximal myocardial activity on the redistribution images. Segments were considered normal if the count variation within the segment was ≤20% compared with the segment with the highest count rate. For the apex and diaphragmatic segments, a range of 30% to 40% was allowed. Ischemia was considered present if the counting rate increased by ≥20% on redistribution images; if the segment activity increased by <20%, scar was considered present. Segments were only considered abnormal if the suspected defect was seen on two or more consecutive slices and could be verified in an orthogonal plane. Although only one reader evaluated each study, that reader was blinded to clinical history, results of prior coronary arteriograms, results of the exercise test (except for peak heart rate) and the hypothesis of this study.

End points. The primary end point was all-cause mortality as assessed by the Social Security Death Index (12). We have described the high specificity and sensitivity of this measure in detail elsewhere (21). The mean follow-up was 6.7 years, with a minimum follow-up among survivors of 4.5 years.

Statistical analyses. Clinical, exercise and scintigraphic abnormalities were related to time-to-death using the Cox proportional hazards model (22). The proportional hazards assumption was verified by inspection of log (-log [survival function]) curves. Unadjusted survival estimates were calculated using the Kaplan-Meier product-limit technique (23), while adjusted survival functions and confidence limits were calculated and plotted based on a likelihood-based approach estimation of the baseline survivorship function (24).

A number of potential nuclear abnormalities have been considered as prognostically important, including the quantity and distribution of scar and ischemic defects (1). To determine how best to characterize perfusion defects for prediction of risk, we used information theory (25), first identifying an optimal model and then determining the most likely parameter estimates (coefficients). Seven potential models were chosen prospectively: 1) the presence of any defect; 2) the presence of any reversible defect; 3) the presence of defects in more than one vascular territory; 4) the total mass of left ventricular myocardium with perfusion defects of any type (on a scale of 0 to 24), in effect, a modified summed stress score (1); 5) the total mass of scar; 6) the total mass of ischemia; and 7) a composite of scar and ischemia mass, with each type of abnormality considered and weighted differently.

To determine which model was best, Akaike Information Criterion (25,26) values and weights were calculated for each model. As shown in Table 1, the best model was the composite of the masses of scar and ischemia, with a 92% probability of best fit. This was verified by performing a series of 100 bootstrap resamplings and Cox modeling for variable selection; the composite model was chosen as best 94% of the time. The bootstrap resamplings approach has been shown to be more efficient for model validation than the simple identification of separate "test" and "validation" datasets (27,28).

To determine parameter coefficients, 500 bootstrap resamplings were performed, and a composite prognostic nuclear score was derived from the resulting median values of each beta coefficient from the Cox regression model. The score was calculated as: score = scar mass + 0.5 (ischemia mass). We prospectively divided subjects into patients with normal scans (score = 0), patients with intermediate risk

Table 1. Thallium SPECT Models for Prediction of All-cause Mortality With Akaike Information Criterion Scores and Weights

Model (Variables)	Hazard Ratio (95% CI)	Δ_i*	ω_i†
Any defect	1.99 (1.74 to 2.28)	32.0	< 0.01
Any ischemia	1.46 (1.24 to 1.72)	113.5	< 0.01
Defects involving more than one vascular territory	1.64 (1.35 to 1.98)	110.5	< 0.01
Total sum score:			
1) Each additional abnormal mass unit (of a possible 24)	1.08 (1.07 to 1.09)	5.0	0.08
Total scar mass:			
1) Each additional mass unit of scar (of a possible 24)	1.09 (1.08 to 1.11)	12.3	< 0.01
Total ischemic segments:			
1) Each additional mass unit of ischemia (of a possible 24)	1.05 (1.02 to 1.08)	120.1	< 0.01
Composite scar and ischemia:			
1) Each additional mass unit of scar	1.09 (1.08 to 1.11)	0.0	0.92
2) Each additional mass unit of ischemia	1.05 (1.03 to 1.08)		

*Difference between Akaike information criterion (AIC) of given model *i* and AIC of the best model, that is, the model with the lowest AIC value. The AIC is calculated as: AIC = −2*log likelihood + 2 (p + 2), where p is the number of parameters in the model. A value of 0 implies the best model. A low value for Δ_i implies a better fit.

†Akaike weight, which is an estimate of the likelihood that a given model *i* is in fact the best model of the ones studied. Thus, the value of 0.92 for the composite model in the last row suggests that there is a 92% probability that this is the best model. A very low value (e.g., <0.01) suggests that it is very unlikely that the given model *i* is the best model.

The Akaike weight is calculated as:

$$\omega_i = \frac{\exp(-\frac{1}{2}\Delta_i)}{\sum_{i=1}^{R} \exp(-\frac{1}{2}\Delta_i)}$$

scans (abnormal scans but with scores below the 90th percentile, i.e., score >0 and <8) and patients with high-risk scans (scores above the 90th percentile, i.e., score ≥8).

The associations of intermediate- and high-risk composite prognostic nuclear scores with mortality were assessed in several prespecified subgroups, and potential interactions were explored. Particular attention was paid a priori to subgroups with impaired physical fitness, abnormal heart rate recovery or both, along with whether or not prior revascularization had been performed.

Multivariable models were used to assess the independent association of intermediate- and high-risk nuclear scores. The results were validated by two series of bootstrapping resamplings (27,29,30), with consideration of variable selection first and determination of parameter coefficients for variables that entered at least 50% of models second. A p value of <0.05 was required for variable retention. No variables were forced. We only considered variables available to clinicians at the time of the stress test. All analyses were performed using the SAS 6.12 system (SAS, Inc., Cary, North Carolina).

RESULTS

Baseline and exercise characteristics. The number of patients who were eligible was 7,163 (age 60 ± 10, 25% women). Thallium SPECT abnormalities were present in 2,817 patients (39%); reversible defects were noted in 1,201 (17%). Based on their composite nuclear prognostic score, patients were classified as low-risk, intermediate-risk and high-risk in 62%, 28% and 10% of cases. Fair or poor physical fitness was found in 2,674 patients (37%); an abnormal heart rate recovery of ≤12 beats/min was present in 2,612 patients (37%).

Baseline clinical and exercise characteristics according to the composite prognostic nuclear score are summarized in Table 2. Compared with patients with low-risk or intermediate-risk composite prognostic nuclear scores, patients with high-risk scores were older, more likely to be men and more likely to have diabetes, Q-waves, a history of prior coronary bypass surgery, more likely to be taking digoxin or beta-blockers and were more likely to have impaired physical fitness or an abnormal heart rate recovery.

Thallium SPECT perfusion defects and mortality. During 47,717 person-years of follow-up, there were 855 deaths. Compared with patients with normal nuclear scans who had a seven-year death rate of 9%, patients with intermediate- and high-risk nuclear scores had increased death rates of 14% and 24% (hazard ratios for intermediate- and high-risk scans 1.67, 95% confidence interval [CI]: 1.44 to 1.95 and 2.98, 95% CI: 2.49 to 3.56). Hazard ratios according to nuclear score in a number of prespecified

Table 2. Baseline and Exercise Characteristics According to Composite Prognostic Nuclear Score

Characteristics	Low Risk (n = 4,433)	Intermediate Risk (n = 1,989)	High Risk (n = 741)
Age (yrs)	59 ± 11	61 ± 10	62 ± 10
Women	1,524 (34%)	211 (11%)	74 (10%)
Resting systolic BP (mm Hg)	137 ± 19	139 ± 20	137 ± 19
Resting heart rate (beats/min)	76 ± 13	74 ± 13	75 ± 12
Hypertension	1,968 (44%)	968 (49%)	353 (47%)
Diabetes	511 (12%)	293 (15%)	134 (18%)
Current smoking	525 (12%)	227 (11%)	78 (11%)
Chronic lung disease	111 (3%)	52 (3%)	18 (2%)
Q-wave on ECG	285 (6%)	472 (24%)	429 (58%)
Left ventricular hypertrophy*	125 (3%)	113 (6%)	55 (7%)
Left bundle branch block	57 (1%)	58 (3%)	37 (5%)
Right bundle branch block	98 (2%)	62 (3%)	31 (4%)
Atrial fibrillation	65 (1%)	31 (2%)	15 (2%)
Prior coronary bypass	755 (17%)	659 (33%)	322 (44%)
Prior percutaneous procedure	602 (14%)	424 (21%)	170 (23%)
Beta-blocker	700 (16%)	483 (24%)	218 (29%)
Calcium blocker	1,488 (34%)	966 (49%)	336 (45%)
Dihydropyridine	476 (11%)	311 (16%)	119 (16%)
ACE inhibitor	347 (8%)	151 (8%)	67 (9%)
Diuretic	723 (16%)	275 (14%)	145 (20%)
Digoxin	271 (6%)	156 (8%)	131 (18%)
Exercise capacity (METS)	8.4 ± 2.4	8.2 ± 2.4	7.6 ± 2.3
Impaired fitness	1,516 (34%)	781 (39%)	377 (51%)
Heart rate recovery (beats/min)	18 ± 8	17 ± 8	17 ± 8
Abnormal heart rate recovery	1,572 (35%)	726 (37%)	314 (42%)

*By ECG.
ACE = angiotensin-converting enzyme; BP = blood pressure; ECG = electrocardiogram; METS = metabolic equivalents.

subgroups were similar. An interaction was noted whereby high-risk scans were less predictive in patients taking beta-blockers (hazard ratios: 1.87 vs. 3.45, p for interaction: 0.004).

Figure 1 shows seven-year mortality according to the number of exercise abnormalities and nuclear scores among patients who had not undergone prior revascularization. Patients who were physically fit and who had normal heart rate recovery were at low risk (<1% per year), irrespective of nuclear score. Conversely, patients who were both physically unfit and who had an abnormal heart rate recovery were at very high risk for death (>3% per year), even with normal nuclear findings. Patients who had either impaired physical fitness or an abnormal heart rate recovery, but not both, had intermediate to high risks for death, depending on the nuclear score. Figures 2 and 3 show analogous seven-year mortality among patients who had undergone prior coronary artery bypass grafting or prior percutaneous intervention (but without prior bypass grafting). Within each of the three exercise groups, abnormal nuclear scans were associated with increased risk.

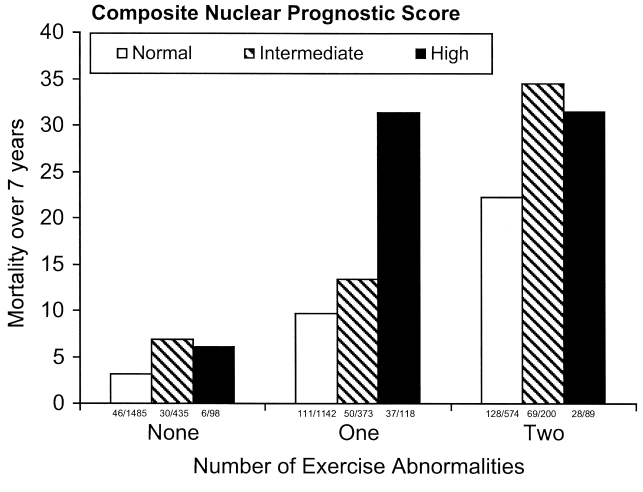

Figure 1. Seven-year mortality according to exercise test findings and composite prognostic nuclear score among patients without a history of prior revascularization. On the horizontal axis, "None" refers to patients with at least average physical fitness and normal heart rate recovery; "One" refers to patients with impaired physical fitness or abnormal heart rate recovery, but not both; and "Two" refers to patients with both impaired physical fitness and an abnormal heart rate recovery. The numbers underneath each of the bars refers to the number of deaths (numerator) and the total number of patients (denominator) in each subgroup.

Multivariable analyses. After adjusting for age; gender; resting blood pressure and heart rate; hypertension; diabetes; smoking; chronic lung disease; ECG findings including Q waves, left ventricular hypertrophy, left and right bundle branch block and atrial fibrillation; prior coronary bypass grafting; prior percutaneous revascularization; use of medications including aspirin, lipid-lowering drugs, beta-blockers, nondihydropyridine and dihydropyridines calcium channel blockers, angiotensin-converting enzyme inhibitors, vasodilators, diuretics and digoxin; functional capacity; heart rate recovery and interaction terms, an intermediate risk nuclear score remained associated with increased risk of

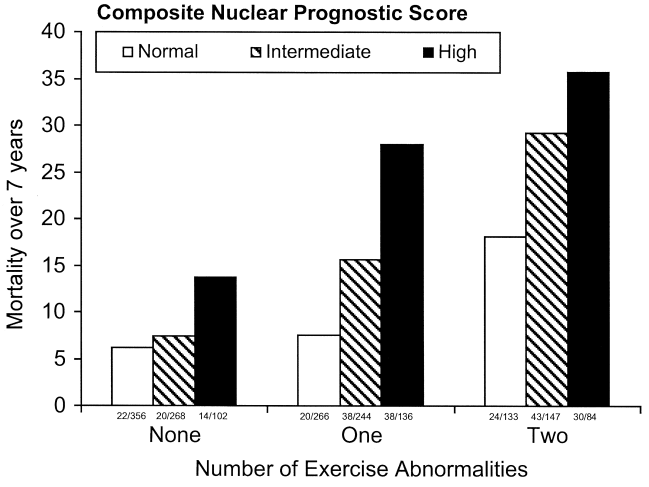

Figure 2. Seven-year mortality according to exercise test findings and composite prognostic nuclear score among patients with a history of prior coronary artery bypass grafting. Horizontal axis labeling is the same as in Figure 1.

death, as was a severe-risk score (Table 3). Other independent predictors of death included fair or poor physical fitness and an abnormal heart rate recovery. Covariate-adjusted survival functions according to nuclear scan results are shown in Figure 4.

To validate these results, a series of bootstrap resamplings with repetitive Cox proportional hazards modeling were performed. First, 100 resamplings for variable selection found that variables that entered models at least 90% of the time included high-risk nuclear score (100%), age (100%), abnormal heart rate recovery (100%), smoking (100%), use of digoxin (99%), intermediate nuclear score (99%) and diabetes (94%). A second set of 500 bootstrap resamplings that adjusted for these variables along with others that entered at least 50% of models demonstrated virtually identical adjusted hazard ratios (for intermediate-risk score adjusted hazard ratio: 1.50, 95% CI: 1.25 to 1.78; for high-risk score adjusted hazard ratio: 2.91, 95% CI: 2.24 to 3.72).

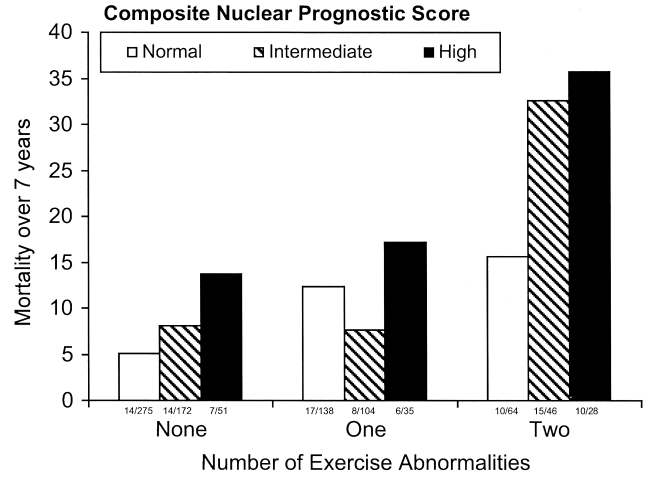

Figure 3. Seven-year mortality according to exercise testing findings and composite prognostic nuclear score among patients with a history of prior percutaneous coronary interventions, but no history of prior coronary bypass grafting. Horizontal axis labeling is the same as in Figure 1.

Table 3. Nuclear and Exercise Predictors of Risk of Death After Adjustment for Potential Confounders: Results of Multivariable Cox Regression Analyses*

Variables	Adjusted Hazard Ratio	95% Confidence Interval	p Value
Intermediate-risk nuclear scan	1.50	1.28 to 1.76	< 0.0001
High-risk nuclear scan	2.76	2.13 to 2.56	< 0.0001
Poor or fair fitness	2.34	2.00 to 2.76	< 0.0001
Abnormal heart rate recovery	1.60	1.37 to 1.87	< 0.0001

*Covariates are listed in text.

DISCUSSION

Main findings. In this large cohort of patients referred for symptom-limited exercise treadmill thallium^{201} SPECT testing, myocardial perfusion defects were independently predictive of long-term all-cause mortality, even after accounting for clinical differences, exercise capacity and heart rate recovery. Using information theory methods (25), we identified a composite model that incorporated both evidence of scar and ischemia as being best for prediction of death.

Because of the long period of follow-up (mean of 6.7 years with a minimum of 4.5 years for survivors) and the large number of outcome events (855 deaths), it was possible to carefully assess the relative associations of nuclear abnormalities and exercise test findings as risk predictors. Among patients who had not undergone prior revascularization (Fig. 1), exercise test findings could identify low-risk (<1% per year) and high-risk (>3% per year) groups with little additional prognostic information provided by nuclear findings. Those patients who had either impaired functional

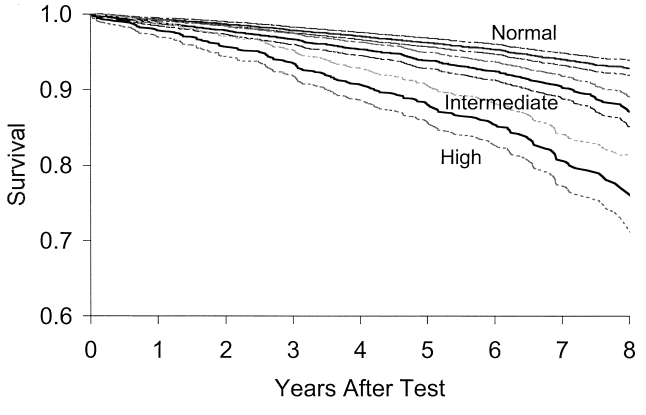

Figure 4. Survival according to thallium^{201} single photon emission computed tomography findings after adjustments for covariates. Patients were classified as having normal scans or scans with intermediate- or high-risk findings based on the composite prognostic nuclear score discussed in detail in the text. **Dotted lines** indicate 95% confidence limits.

capacity or an abnormal heart rate recovery, but not both, represented an intermediate-risk group for whom the nuclear test was particularly useful in stratifying risk, consistent with the Bayesian theory (31).

Previous reports. A number of groups have demonstrated prognostic associations between nuclear perfusion abnormalities and cardiac events (1,4). This study expounds upon these in several respects. First, we found that nuclear findings predict all-cause death. As has been discussed elsewhere (10,11), the end point of "cardiac death" is inherently suspect due to poor quality, biased recording of death certificates and complexities of human disease (32). All-cause death is a relevant end point in a cardiac population, as shown in clinical trials in which an intervention designed to treat cardiac disease resulted in reductions in all-cause mortality (33).

Second, instead of comparing the nuclear scan with the exercise electrocardiogram or the Duke treadmill score (16,17), we compared it against functional capacity and heart rate recovery; exercise findings are among the strongest predictors of risk and are available in nearly all patients, regardless of medication use or baseline electrocardiographic abnormalities. Third, because of the large size of the cohort and number of events, we could do robust subgroup analyses of the prognostic usefulness of nuclear imaging among patients with and without exercise test abnormalities.

Study limitations. The scintigraphic methods used in our laboratory in the early 1990s (18,19) are not representative of the most modern techniques available. Newer isotopes, better acquisition protocols (34), gated SPECT imaging (35) and attenuation correction (36) may mean that nuclear images obtained now may have better prognostic value. By studying patients who were imaged in the early 1990s, however, we were able to analyze the impact of nuclear findings on long-term outcome.

Defect severity for each segment was not examined in the analysis. Whether defect severity might have had an impact on our study is uncertain. It is possible that measures of defect extent and severity might have both contributed to the prognostic value of imaging. There are certain inherent limitations with SPECT imaging techniques that fundamentally limit the ability to ascertain actual perfusion defect severity (37).

Segments thought to represent attenuation were considered normal. This was the most conservative approach as the appearance of artifacts may be surrogates for comorbid conditions and elevate event rates in patients classified as normal. Body mass index was not available. Exactly how consideration of attenuation might have affected the prognostic model is not entirely clear, as attenuation defects may also be associated with leanness, which may itself be associated with reduced mortality (38).

Other limitations are that our study was performed at a single tertiary care center, leading to possible biases of patient selection. We used bootstrapping to provide relatively unbiased low-variance estimates of prediction without having to sacrifice data for model development (28). Nonetheless, confirmation of our results on entirely independent external datasets is essential. We were unable to perform detailed analyses of left ventricular dilation and increased lung uptake of thallium. Formal measures of left ventricular function were not available. We did exclude patients with known heart failure or left ventricular systolic dysfunction, though, and we accounted for use of digoxin and diuretics in our multivariable analyses.

Conclusions. Despite these limitations, we found that myocardial perfusion abnormalities as assessed by thallium^{201} SPECT imaging are powerful and independent predictors of long-term all-cause mortality. The value of exercise nuclear imaging for risk stratification is particularly enhanced when exercise capacity and heart rate recovery are also considered.

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REFERENCES

1. Hachamovitch R, Berman DS, Shaw LJ, et al. Incremental prognostic value of myocardial perfusion single photon emission computed tomography for the prediction of cardiac death: differential stratification for risk of cardiac death and myocardial infarction (published erratum appears in Circulation 1998;98:190). Circulation 1998;97:535–43.
2. Kaul S, Lilly DR, Gascho JA, et al. Prognostic utility of the exercise thallium-201 test in ambulatory patients with chest pain: comparison with cardiac catheterization. Circulation 1988;77:745–58.
3. Miller TD, Christian TF, Clements IP, Hodge DO, Gray DT, Gibbons RJ. Prognostic value of exercise thallium-201 imaging in a community population. Am Heart J 1998;135:663–70.
4. Lauer MS, Lytle B, Pashkow F, Snader CE, Marwick TH. Prediction of death and myocardial infarction by screening with exercise-thallium testing after coronary artery bypass grafting. Lancet 1998;351:615–22.
5. Machecourt J, Longere P, Fagret D, et al. Prognostic value of thallium-201 single-photon emission computed tomographic myocardial perfusion imaging according to extent of myocardial defect: study in 1,926 patients with follow-up at 33 months. J Am Coll Cardiol 1994;23:1096–106.
6. 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;30:641–8.
7. Wei M, Kampert JB, Barlow CE, et al. Relationship between low cardiorespiratory fitness and mortality in normal weight, overweight and obese men. JAMA 1999;282:1547–53.
8. Cole CR, Blackstone EH, Pashkow FJ, Snader CE, Lauer MS. Heart-rate recovery immediately after exercise as a predictor of mortality. N Engl J Med 1999;341:1351–7.
9. Cole CR, Foody JM, Blackstone EH, Lauer MS. Heart rate recovery following submaximal exercise testing as a predictor of mortality in a healthy cohort. Ann Intern Med 2000;132:552–5.
10. Lauer MS, Blackstone EH, Young JB, Topol EJ. Cause of death in clinical research: time for a reassessment? J Am Coll Cardiol 1999;34:618–20.
11. Gottlieb SS. Dead is dead—artificial definitions are no substitute. Lancet 1997;349:662–3.
12. Curb JD, Ford CE, Pressel S, Palmer M, Babcock C, Hawkins CM. Ascertainment of vital status through the National Death Index and

the Social Security Administration. Am J Epidemiol 1985;121:754–66.
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;281:524–9.
14. Lauer MS, Mehta R, Pashkow FJ, Okin PM, Lee K, Marwick TH. Association of chronotropic incompetence with echocardiographic ischemia and prognosis. J Am Coll Cardiol 1998;32:1280–6.
15. Lauer MS, Okin PM, Larson MG, Evans JC, Levy D. Impaired heart rate response to graded exercise: prognostic implications of chronotropic incompetence in the Framingham Heart study. Circulation 1996;93:1520–6.
16. Mark DB, Shaw L, Harrell FE, Jr, et al. Prognostic value of a treadmill exercise score in outpatients with suspected coronary artery disease. N Engl J Med 1991;325:849–53.
17. Kwok JM, Miller TD, Christian TF, Hodge DO, Gibbons RJ. Prognostic value of a treadmill exercise score in symptomatic patients with nonspecific ST-T abnormalities on resting ECG. JAMA 1999; 282:1047–53.
18. Go RT, Marwick TH, MacIntyre WJ, et al. A prospective comparison of rubidium-82 PET and thallium-201 SPECT myocardial perfusion imaging utilizing a single dipyridamole stress in the diagnosis of coronary artery disease. J Nucl Med 1990;31:1899–905.
19. Lauer MS, Pashkow FJ, Snader CE, Harvey SA, Thomas JD, Marwick TH. Gender and referral for coronary angiography after treadmill thallium testing. Am J Cardiol 1996;78:278–83.
20. Go RT, MacIntyre WJ, Cook SA, et al. The incidence of scintigraphically viable and nonviable tissue by rubidium-82 and fluorine-18-fluorodeoxyglucose positron emission tomographic imaging in patients with prior infarction and left ventricular dysfunction. J Nucl Cardiol 1996;3:96–104.
21. 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: 1392–8.
22. Cox D. Regression models and life tables (with discussion). J R Stat Soc B 1972;34:187–220.
23. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457–81.
24. Lawless JF. Statistical Models and Methods for Lifetime Data. New York, NY: John Wiley and Sons, 1982.
25. Burnham KP, Anderson DR. Model Selection and Inference: A Practical Information Theoretic Approach. New York: Springer, 1998.
26. Akaike H. A Bayesian analysis of the minimum AIC procedure. Ann Inst Stat Math 1978;30:9–14.
27. Efron B. Estimation the error rate of a prediction rule: improvement on cross-validation. J Am Stat Assoc 1983;78:316–331.
28. Harrell FE, Jr, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy and measuring and reducing errors. Stat Med 1996;15:361–87.
29. Collett D, Stepniewska K. Some practical issues in binary data analysis. Stat Med 1999;18:2209–21.
30. Chen CH, George SL. The bootstrap and identification of prognostic factors via Cox's proportional hazards regression model. Stat Med 1985;4:39–46.
31. Eagle KA, Coley CM, Newell JB, et al. Combining clinical and thallium data optimizes preoperative assessment of cardiac risk before major vascular surgery. Ann Intern Med 1989;110:859–66.
32. Lloyd-Jones DM, Martin DO, Larson MG, Levy D. Accuracy of death certificates for coding coronary heart disease as the cause of death. Ann Intern Med 1998;129:1020–6.
33. Randomized trial of cholesterol lowering in 4,444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994;344:1383–9.
34. Berman DS, Kiat H, Friedman JD, et al. Separate acquisition rest thallium-201/stress technetium-99m sestamibi dual-isotope myocardial perfusion single-photon emission computed tomography: a clinical validation study. J Am Coll Cardiol 1993;22:1455–64.
35. Smanio PE, Watson DD, Segalla DL, Vinson EL, Smith WH, Beller GA. Value of gating of technetium-99m sestamibi single-photon emission computed tomographic imaging. J Am Coll Cardiol 1997; 30:1687–92.
36. Prvulovich EM, Lonn AH, Bomanji JB, Jarritt PH, Ell PJ. Effect of attenuation correction on myocardial thallium-201 distribution in patients with a low likelihood of coronary artery disease. Eur J Nucl Med 1997;24:266–75.
37. Eisner RL, Patterson RE. The challenge of quantifying defect size and severity: reality versus algorithm (editorial). J Nucl Cardiol 1999;6: 362–71.
38. Calle EE, Thun MJ, Petrelli JM, Rodriguez C, Heath CW, Jr. Body mass index and mortality in a prospective cohort of U.S. adults. N Engl J Med 1999;341:1097–105.