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Normal Stress-Only Versus Standard Stress/Rest Myocardial Perfusion Imaging

Similar Patient Mortality With Reduced Radiation Exposure

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Objectives The aim of this study was to determine whether a normal stress-only single-photon emission computed tomographic myocardial perfusion tomography (SPECT) study confers the same prognosis as a normal SPECT on the basis of evaluation of stress and rest images.

Background Current guidelines recommend stress and rest imaging to confirm that a SPECT study is normal.

Methods We determined all-cause mortality in 16,854 consecutive patients who had a normal gated stress SPECT. Median follow-up was 4.5 years. A stress-only protocol was used in 8,034 patients (47.6%), whereas 8,820 (52.4%) had both stress and rest imaging.

Results The overall unadjusted annual mortality rate in patients who had a normal SPECT with a stress-only protocol was lower than in those who required additional rest imaging (2.57% vs. 2.92%, $p = 0.02$). After adjustment for baseline clinical characteristics no significant differences in patient mortality were seen between the 2 imaging protocols, but the stress-only group received a 61% lower radiopharmaceutical dosage. Independent predictors of worse survival included increasing age, male sex, diabetes, history of coronary artery disease, and inability to exercise (all $p < 0.001$) but not the type of SPECT protocol used to image patients.

Conclusions Patients determined to have a normal SPECT on the basis of stress imaging alone have a similar mortality rate as those who have a normal SPECT on the basis of evaluation of both stress and rest images. Our results support that additional rest imaging is not required in patients who have a normally appearing initial stress study. A significant reduction in radiation exposure can be achieved with such an approach. (J Am Coll Cardiol 2010; 55:221–30) © 2010 by the American College of Cardiology Foundation

Stress single-photon emission computed tomographic myocardial perfusion imaging (SPECT) performed with technetium (Tc)-99m–labeled radiopharmaceuticals is widely used for diagnosing coronary artery disease (CAD) and assessing patient risk (1). With an aging population and the constantly increasing number of individuals at risk for CAD, the annual number of SPECT studies performed is likely to further increase. This reality is juxtaposed with a heightened national emphasis on cost containment, improving laboratory efficiency, and reducing radiation exposure from medical imaging (2,3).

Current SPECT imaging guidelines with Tc-99m tracers recommend acquiring images after stress and again at rest (4). This typically requires a patient to spend 4 to 5 h in the laboratory for 2 imaging sessions or return the following day for rest imaging. As an alternative strategy, we have advocated for over 1 decade a stress imaging protocol followed by rest imaging only in patients with equivocal or clearly abnormal studies. The advantages of such an approach are to substantially reduce radiation exposure, lower costs by eliminating unnecessary imaging time and radiopharmaceutical doses, and improve laboratory efficiency by freeing up camera time to study additional patients.

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Concern has been raised, however, over the safety of such an imaging strategy (5) with little available data to provide reassurance (6). Thus, the purpose of this study was to examine whether patients with a normal SPECT on the basis of evaluation of stress imaging alone would have the same long-term outcome as patients who have a normal SPECT on the basis of interpretation of both stress and rest images.

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Abbreviations and Acronyms

BMI = body mass index

CAD = coronary artery disease

ECG = electrocardiogram

LV = left ventricular

LVEF = left ventricular ejection fraction

SPECT = single-photon emission computed tomography

Tc = technetium

TR = time ratio

Methods

Study population. From December 1999 to December 2007, 27,540 consecutive patients at our institution underwent stress SPECT with Tc-99m radiotracers for clinically indicated reasons. This report focuses on the 16,854 patients (61%) in whom the SPECT study was interpreted as normal. This percentage of patients with normal study results is similar to that reported in other large trials (7,8) and meta-analysis studies (9).

Gated stress SPECT imaging protocol. Gated SPECT was performed according to American Society of Nuclear Cardiology guidelines with either Tc-99m sestamibi (83.5%) or Tc-99m tetrofosmin (16.5%) as the radiotracer (4). The routine protocol in our laboratory is to perform stress imaging first as either: 1) a same-day low-dose stress (8 to 15 mCi)/high-dose rest (25 to 40 mCi) procedure; or 2) a 2-day high-dose stress/high-dose rest procedure in patients weighing >200 lbs or in women with a >C breast cup size. Rest imaging is performed before stress imaging (2-day rest-stress protocol) only when a patient presents to the laboratory late in the afternoon or reports caffeine intake within 12 h and is scheduled for pharmacologic stress.

Treadmill exercise was used as the stressor in 5,487 patients (32.6%), whereas 11,367 (67.4%) received either adenosine (n = 10,601 or 62.9%) or dobutamine (n = 766 or 4.5%) with standard infusion protocols (4). All exercise electrocardiograms (ECGs) were interpreted in conjunction with the SPECT images. An ischemic ECG response was defined as a ≥1-mm ST-segment depression occurring >80 ms after the J point. The Duke treadmill score was calculated in all patients undergoing exercise stress and defined as low (≥5), intermediate (−10 to 4), or high (≤−11) risk (10).

After study acquisition, stress SPECT images were reconstructed and reoriented according to American Society of Nuclear Cardiology guidelines and then visually reviewed in all 3 standard cardiac projections along with the gated SPECT and raw image data (11). Attenuation correction was performed in all studies with either a transmission source (Vantage, Phillips FORTE, Best, the Netherlands) or a computed tomography image (Phillips Precedence SPECT/CT system). Quantitative SPECT was also performed by an experienced nuclear cardiologist (J.J.M., or the late Mario S. Verani, MD) with a previously validated, automated program to determine the total and ischemic left ventricular (LV) perfusion defect size (12).

Procedure for study interpretation. After study acquisition, all stress images were interpreted on the basis of integration of the rotating raw projection data, the reoriented tomographic perfusion images, the gated SPECT information, and the quantitative SPECT perfusion results. A study was interpreted as normal if perfusion was assessed to be homogeneous throughout the myocardium, LV cavity size was normal, the left ventricular ejection fraction (LVEF) was ≥50% with normal regional wall motion, and the quantified perfusion defect size was 0% at 2.5 SDs. Subsequent rest imaging was performed if the stress images did not fulfill these criteria and were therefore deemed to be either abnormal or equivocal. Attenuation-corrected images were reviewed only to confirm that a study was normal but were not otherwise used in the decision process. Likewise, the stress ECG results were not used to determine whether a patient with a normal stress perfusion study needed rest imaging.

Follow-up and outcomes. In April 2009 all patients had assessment of their vital status through the Social Security Death Index. Mean follow-up was 4.76 years (median 4.5 years, 25th and 75th percentiles: 2.68 and 6.6 years, respectively). The minimal follow-up duration was 16 months for those without an event.

Statistical analysis. Continuous variables are expressed as mean ± SD, and categorical variables are expressed as frequency (percentage). The patient's pre-test likelihood for CAD was determined with the standard Diamond criteria with the assumption that chest pain was atypical (13). Baseline patient characteristics were examined according to SPECT protocol. The Student *t* test was employed to identify mean differences for continuous variables between SPECT protocols. Contingency table analysis was performed with chi-square tests. Kaplan-Meier analysis of all-cause mortality was performed. Time 0 was defined as the date of SPECT imaging. The 2-sided log-rank tests were used to determine significance. Univariate and multivariate analyses were used to identify the association between time-to-event and baseline clinical characteristics between the 2 SPECT protocols. Clinical characteristics included in the model were: age; sex; body mass index (BMI); history of CAD, smoking, hyperlipidemia, hypertension, and diabetes mellitus; chest pain symptoms and stress ECG results; and the stress modality used in conjunction with SPECT.

The primary end point in this study was total mortality. The statistical plan was based on the following considerations. If time to death is not available, a logistic model is used to estimate an odds ratio to assess relative risk of death between groups. If time to death is available, then a Cox proportional hazards model is used to estimate the hazard ratio assuming the proportional hazard is not violated. The Cox proportional hazard model assumes that the hazard function for an individual (i.e., observation in the analysis) depends on the values of the covariates and the value of the baseline hazard. Given 2 individuals with particular values for the covariates, the ratio of the estimated hazards over time should be constant. When this assumption is violated,

Table 1 Baseline Demographic and Stress Information

Clinical Characteristics	Total (n = 16,854)	Stress-Only (n = 8,034)	Stress and Rest (n = 8,820)	p Value
Age (yrs)	59.2 ± 13	59.8 ± 13	58.7 ± 13	<0.001
Female sex	9,430 (56.0%)	5,073 (63.1%)	4,357 (49.4%)	<0.001
Mean number of risk factors	1.44 ± 1.1	1.37 ± 1.1	1.51 ± 1.1	<0.001
Diabetes mellitus	4,545 (27.0%)	2,058 (25.6%)	2,487 (28.2%)	<0.001
Hypertension	10,832 (64.3%)	5,020 (62.5%)	5,812 (65.9%)	<0.001
Hyperlipidemia	6,607 (39.2%)	3,029 (37.7%)	3,578 (40.6%)	<0.001
Smoking	1,889 (11.2%)	730 (9.1%)	1,159 (13.1%)	<0.001
History of MI	565 (3.4%)	210 (2.6%)	355 (4.0%)	<0.001
History of CAD*	4,562 (27.1%)	1,960 (24.4%)	2,602 (29.5%)	<0.001
Mean BMI (kg/m^2)	28.9 ± 5.9	27.8 ± 5.2	29.8 ± 6.4	<0.001
<20	214 (1.3%)	129 (1.6%)	85 (1.0%)	<0.001
20–25	3,085 (18.3%)	1,668 (20.7%)	1,417 (16.1%)	<0.001
25–30	8,015 (47.5%)	3,604 (44.9%)	4,411 (50.0%)	<0.001
>30	5,540 (32.9%)	2,633 (32.8%)	2,907 (33.0%)	<0.001
Indications for SPECT				
Chest pain	12,281 (72.9%)	5,593 (69.6%)	6,688 (75.8%)	<0.001
Exertional dyspnea	994 (5.9%)	506 (6.3%)	488 (5.5%)	0.04
Pre-operative clearance	2,010 (11.9%)	1,073 (13.4%)	937 (10.6%)	<0.001
Inpatient status	5,271 (31.3%)	2,524 (31.4%)	2,747 (31.1%)	0.7
Stressor used				
Exercise stress	5,487 (32.5%)	3,062 (38.1%)	2,425 (27.5%)	<0.001
Pharmacologic stress	11,367 (67.5%)	4,972 (61.9%)	6,395 (72.5%)	<0.001
Tc-99m tracer used				
Sestamibi	14,071 (83.5%)	6,975 (86.8%)	7,096 (80.5%)	<0.001
Tetrofosmin	2,783 (16.5%)	1,059 (13.2%)	1,724 (19.5%)	<0.001
Mean Duke treadmill score				
Low risk	4,280 (78.0%)	2,318 (75.7%)	1,962 (80.9%)	<0.001
Intermediate risk	1,207 (22.0%)	744 (24.3%)	463 (19.1%)	<0.001
Ischemic stress ECG	1,315 (7.8%)	733 (9.1%)	582 (6.6%)	<0.001
LVEF	66 ± 8%	66.5 ± 8.6%	65.5 ± 8.3%	<0.001

Values are mean ± SD or n (%). *Prior myocardial infarction (MI) or history of coronary revascularization.
BMI = body mass index; CAD = coronary artery disease; ECG = electrocardiography; LVEF = left ventricular ejection fraction; SPECT = stress myocardial perfusion tomography; Tc = technetium.

then accelerated failure time models are used to derive the time ratio (TR).

Because the Cox proportional hazard assumption was violated in our study, accelerated failure time models were used to determine the best distribution fitted to time to event on the basis of Akaike information criteria. The best distribution was identified with the generalized gamma distribution model, and this was used to calculate the TR. A TR >1 defines an increase in survival time, whereas a TR <1 defines a decrease in survival time. For example, a TR of 2 implies that survival time is significantly prolonged (doubled) among patients with a given predictor versus those without it. Conversely, a TR of 0.5 indicates a 50% reduction in survival time in patients with/without a specific predictor. A Type I error of alpha = 0.05 was used for all hypothesis testing. All statistical analyses were performed with STATA version 10 (StataCorp, College Station, Texas).

Results

Baseline characteristics. For the entire cohort of 16,854 patients with a normal SPECT, the mean age was 59.2 years (range 16 to 100 years, interquartile range 50 to 69 years), approximately one-half were female, 27% were diabetic, and 31% had a history of CAD or myocardial infarction (Table 1). In the 69% of patients without known CAD, most (n = 6,764 or 58%) had at least an intermediate pre-test likelihood for CAD. The major indications for SPECT were evaluation of chest pain or exertional dyspnea and pre-operative clearance. Other indications were for evaluation of an abnormal ECG (5%), syncope (2.5%), new onset atrial fibrillation/flutter (0.8%), an abnormal stress test (0.8%), and ventricular tachycardia (0.1%). Most patients underwent pharmacologic stress testing, and one-third were inpatients. The Duke treadmill score was low-risk in most patients, and the mean LVEF by gated SPECT was 66%.

There were significant differences in the baseline characteristics of patients who underwent stress-only imaging versus those who had additional rest imaging. The stress-only group was older, more commonly female, less likely to have diabetes or a history of CAD, and had a lower BMI than those requiring additional rest imaging (all $p < 0.001$). A larger percentage of patients in the

Table 2 SPECT Protocol and Tc-99m Radiopharmaceutical Doses

	Total (n = 16,854)	Stress-Only (n = 8,034)	Stress and Rest (n = 8,820)	p Value
Tc-99m dose (mCi)	39 ± 20	21.3 ± 10.7	55.1 ± 11.9	<0.001
Stress-only protocol				
1. Low-dose stress-only	4,948 (29.4%)	4,948 (61.6%)		
Tc-99m dose (mCi)	13.5 ± 2	13.5 ± 2	55.1 ± 11.9	<0.001
2. High dose stress-only	3,086 (18.3%)	3,086 (38.4%)		
Tc-99m dose (mCi)	33.8 ± 6.2	33.8 ± 6.2	55.1 ± 11.9	<0.001
Stress and rest protocol				
1. Same day low-dose/high-dose stress with rest	5,869 (34.8%)		5,869 (66.5%)	
Tc-99m dose (mCi)	49.6 ± 4.9		49.6 ± 4.9	
2. 2-day low-dose stress with low-dose rest	217 (1.3%)		217 (2.5%)	
Tc-99m dose (mCi)	28.3 ± 3.6		28.3 ± 3.6	
3. 2-day high-dose stress with high-dose rest	2,734 (16.2%)		2,734 (31.0%)	
Tc-99m dose (mCi)	68.9 ± 9.4		68.9 ± 9.4	

Values are mean ± SD or n (%).
Abbreviations as in Table 1.

stress-only group had exercise as the stressor modality ($p < 0.001$).

Impact of SPECT protocol on radiopharmaceutical dose. The SPECT protocols used and the associated radiopharmaceutical doses administered to patients are shown in Table 2. The mean Tc-99m dose received by patients in the entire cohort was 39 ± 20 mCi. A low- or high-dose stress-only protocol was performed in 8,034 patients (47.7%), whereas additional rest images were acquired in 8,820 (52.3%). Among the latter group, rest imaging was performed before stress in 3,858 (43.7%).

In the stress-only group, the mean radiopharmaceutical dosage was significantly lower as compared with those who required additional rest imaging ($p < 0.001$). This was particularly true in the 29.4% of patients who only received a low dose of radiopharmaceutical at stress.

Mortality rates on the basis of SPECT protocol in all patients and specific subgroups. For the entire cohort of 16,854 patients, there were 2,164 deaths (12.84%) over a mean follow-up of 4.76 years (unadjusted annualized event rate 2.74%). Mortality rates with a normal SPECT were significantly higher in patients who were older versus younger, diabetic versus nondiabetic, nonobese versus obese, and inpatients versus outpatients (Table 3). This was also true in patients with versus without CAD, those who underwent pharmacologic stress versus treadmill exercise, and patients with an intermediate- versus a low-risk Duke treadmill score (Table 3).

In the stress-only group there were 1,042 deaths (12.96%) over 5.05 ± 2.5 years (annualized unadjusted mortality rate 2.57%) versus 1,122 deaths (12.72%) over 4.35 ± 2.2 years (annualized unadjusted mortality rate 2.92%) in the stress and rest imaging group ($p = 0.02$) (Fig. 1). This difference in annual mortality rate was also significant when comparing patients who had stress-only (2.57%) versus either stress-rest (2.94%) or rest-stress (2.9%) imaging ($p = 0.049$). However, statistical significance was lost in all of these comparisons when adjusted for baseline clinical characteristics (Fig. 1). In the stress-only group, there was no difference in mortality on the basis of whether patients received a low or high dose of radiopharmaceutical (unadjusted $p = 0.12$, adjusted $p = 0.34$).

Similar trends were observed among various patient subgroups (Table 3). Patients who had a normal stress-only SPECT had a lower unadjusted annualized morality rate versus those who had additional rest imaging if they were >65 years of age, male, diabetic, had a BMI <30 kg/m^2, and were inpatients. As in the overall analysis, there were no significant differences in patient survival between the imaging protocols after adjustment for baseline clinical characteristics (Table 3, Figs. 2 to 6).

Predictors of mortality. The TR, as an indicator of increasing (i.e., <1) or decreasing (i.e., >1) mortality, is shown in Table 4 for various clinical and imaging variables. Univariate predictors of death included increasing age, low BMI (<20 kg/m^2), history of CAD, dyspnea, the presence of hypertension and diabetes mellitus, history of smoking, inpatient status, and need for pharmacologic stress testing (all $p < 0.001$). Independent predictors of death by multivariate analysis were age, male sex, low BMI (<20 kg/m^2), history of CAD, diabetes mellitus, history of smoking, inpatient status, and need for pharmacologic stress testing (all $p < 0.001$).

A need for rest imaging was a univariate predictor of worse outcome (TR 0.89, $p = 0.03$) but not by multivariate analysis (TR 1.008, 95% confidence interval: 0.906 to 1.12, $p = 0.887$).

Discussion

The current study determined all-cause mortality over a 5-year follow-up period in 16,854 patients who had a normal SPECT study. We found that patients determined to have a normal SPECT on the basis of stress

Table 3 Annualized All-Cause Mortality Rates Between Subgroups

	Total	Stress-Only (n = 8,034)	Stress and Rest (n = 8,820)	p Value	Adjusted* p Value
Age (yrs)					
<65	1.78	1.69	1.87	0.4	0.42
>65	4.85	4.45†	5.28†	0.005†	0.46
	$p < 0.001$				
Sex					
Female	2.65	2.55	2.78	0.32	0.75
Male	2.86	2.60†	3.06†	0.04†	0.99
	$p = 0.07$				
Diabetes mellitus					
No	2.13	2.05	2.22	0.46	0.27
Yes	4.55	4.21†	4.88†	0.04†	0.27
	$p < 0.001$				
Coronary artery disease					
No	2.39	2.29	2.49	0.38	0.58
Yes	3.67	3.39	3.92	0.43	0.61
	$p < 0.001$				
BMI (kg/m^2)					
<30	3.00	2.79†	3.23†	0.03†	0.99
≥30	2.3	2.2	2.43	0.31	0.36
	$p < 0.001$				
Hospital status					
Outpatient	1.87	1.81	1.94	0.35	0.09
Inpatient	4.85	4.45†	5.25†	0.03†	0.13
	$p < 0.001$				
Stressor modality					
Treadmill exercise	0.61	0.55	0.68	0.07	0.38
Pharmacologic stress	4.07	4.19	3.97	0.11	0.78
	$p < 0.001$				
Duke treadmill score					
Low risk	0.49	0.43	0.57	0.10	0.22
Intermediate risk	0.99	0.91	1.14	0.24	0.98
	$p < 0.001$				

*Adjusted on the basis of clinical variables. †Significantly lower all-cause mortality stress-only versus stress and rest imaging cohort.
BMI = body mass index.

imaging alone had a mortality rate similar to those who had a normal SPECT on the basis of evaluation of both stress and rest images. This was true irrespective of patient age, sex, clinical risk factors, history of CAD, or the stressor modality used in conjunction with SPECT. Importantly, the stress-only group represented one-third of all patients imaged in our laboratory over an 8-year time period and almost one-half of all patients interpreted as having a normal study. Of added benefit, there was a significant reduction in the radiopharmaceutical dose received by patients who had stress-only imaging (21.3 ± 10.7 mCi) versus those who underwent additional rest imaging (55.1 ± 11.9 mCi), and this was particularly true in the 62% of patients who received a low dose of Tc-99m on their stress-only exam (13.5 ± 2 mCi). Our results indicate that additional rest imaging is unnecessary in patients with a normally appearing initial stress SPECT. Selectively targeting rest imaging to appropriate patients should lower cost by eliminating unnecessary imaging time and radiopharmaceutical doses, improve laboratory throughput, and significantly lower radiation exposure in a substantial percentage of patients.

Interpreting a stress study as normal. The benefits of stress-only imaging must be weighed against the potential for under-diagnosis of significant CAD, because patients with left main or triple vessel CAD might have a normally appearing stress SPECT or post-stress stunning (5,14). Several recent technical advances over the past decade such as ECG gating, reliable attenuation correction, and quantification of the perfusion images have increased confidence for interpreting a study as normal from the stress images alone. We diagnose a patient as having a normal study only if LV perfusion appears visually homogeneous, cavity size is normal, the ejection fraction is ≥50% with normal regional wall motion, and quantitative analysis shows no perfusion defect at 2.5 SDs. In the study by Berman et al. (14), all patients with significant left main stenosis had some abnormality on their gated stress exam: 97% with a perfusion defect ≥2%, 26% with a low LVEF (<50%),

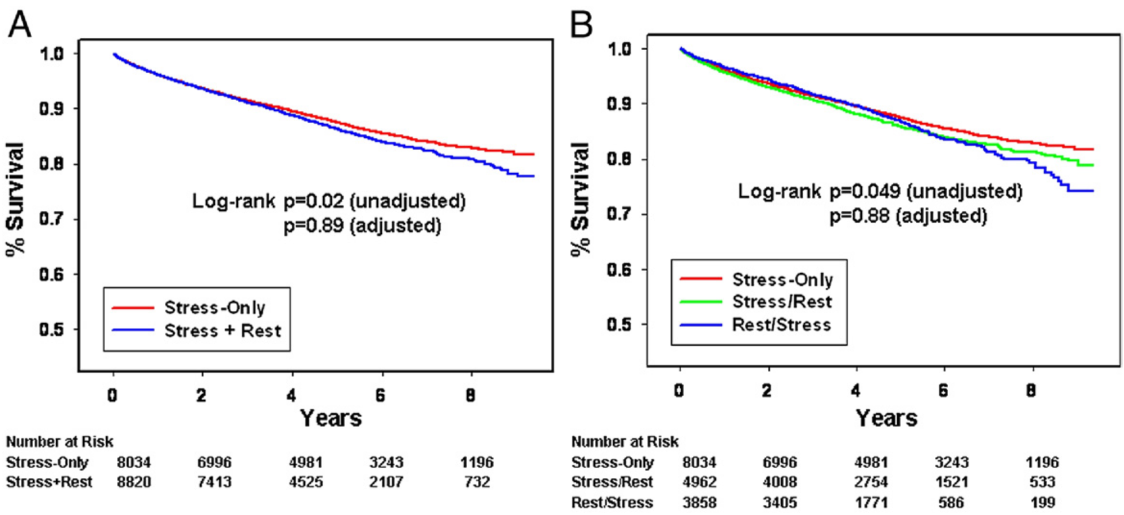

Figure 1 **Survival for the Entire Cohort According to SPECT Protocol**

Survival curves for the entire cohort according to single-photon emission computed tomographic myocardial perfusion imaging (SPECT) protocol on the basis of whether patients with a normal SPECT had stress-only versus additional rest imaging **(A)** or stress-only versus stress-rest or rest-stress imaging **(B)**.

24% with cavity dilation, and 48% with abnormal regional wall motion. Most of our patients with significant CAD would have had rest imaging, on the basis of our strict definition of normal, because of either equivocal stress findings or frankly abnormal results. The comparably low all-cause mortality rates we report in the stress-only and stress-rest cohorts attest to the success of this interpretation algorithm.

Previous studies. There are few published studies addressing the feasibility of stress-only imaging and subsequent patient outcome. Gibson et al. (6) evaluated 652 patients with a low to intermediate probability of CAD who underwent stress-only imaging and were then followed a mean of 22.3 months. Most of the patients (93%) were stressed with treadmill exercise, with the remaining 43 patients receiving dipyridamole. Thirty-seven percent would have required rest imaging but were interpreted as normal on the basis of attenuation-corrected images. The overall cardiac event rate was low at 0.6% with no cardiac deaths and only 1 nonfatal myocardial infarction. Similarly, Gal and Ahmad (15) followed 116 patients after a normal stress-only SPECT with a subsequent 0.9% mortality rate at

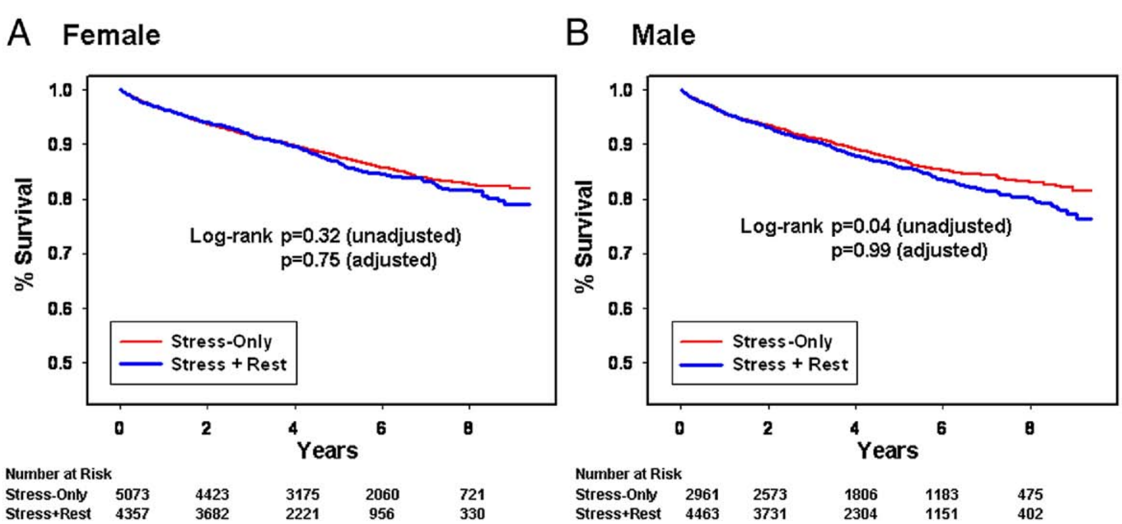

Figure 2 **Survival on the Basis of Sex for Each SPECT Protocol**

Survival curves on the basis of female **(A)** or male **(B)** sex for each single-photon emission computed tomographic myocardial perfusion imaging (SPECT) protocol.

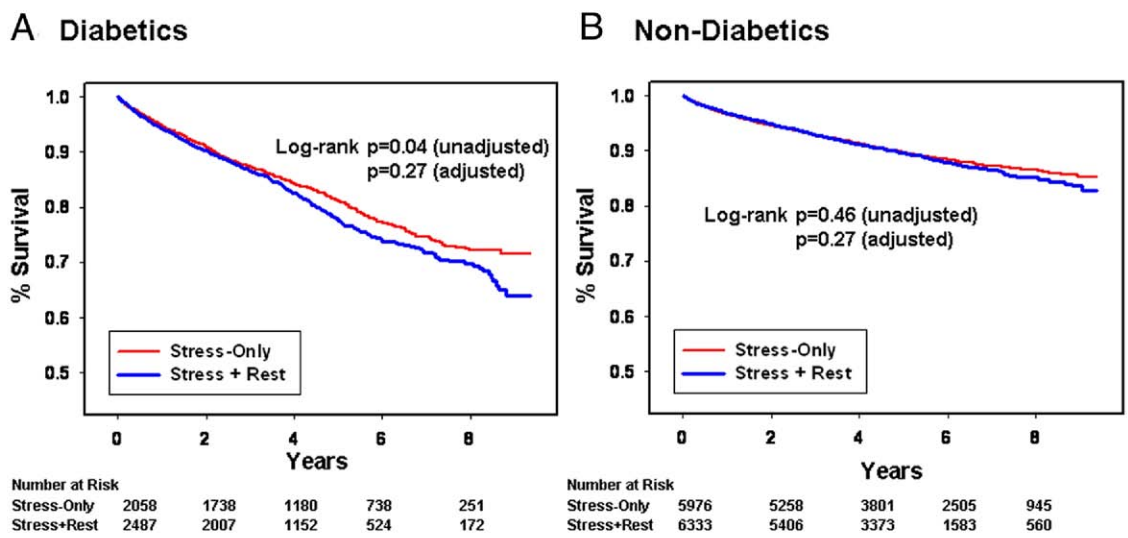

Figure 3 **Survival on the Basis of Diabetic Status for Each SPECT Protocol**

Survival curves on the basis of the presence **(A)** or absence **(B)** of diabetes mellitus for each single-photon emission computed tomographic myocardial perfusion imaging (SPECT) protocol. Diabetic persons had a significantly higher mortality rate than nondiabetic persons, but death rates were similar in the 2 imaging protocols.

1 year. Our study extends these earlier observations by evaluating a very large, diverse consecutive group of patients referred for SPECT imaging. We report a low 0.55% all-cause annual mortality rate, comparable to these smaller studies, among patients who underwent treadmill exercise in conjunction with stress-only imaging. In addition, we showed no survival advantage between the 2 imaging protocols among several clinically important patient subgroups on the basis of age, sex, diabetic status, or history of CAD.

SPECT for risk assessment. Over 2 decades of clinical experience has established the role of stress SPECT in the routine clinical management of patients with suspected or known CAD (1). A normal SPECT generally defines a group with a <1% annual risk for cardiac death and nonfatal myocardial infarction and a low 0.5% cardiac mortality (9).

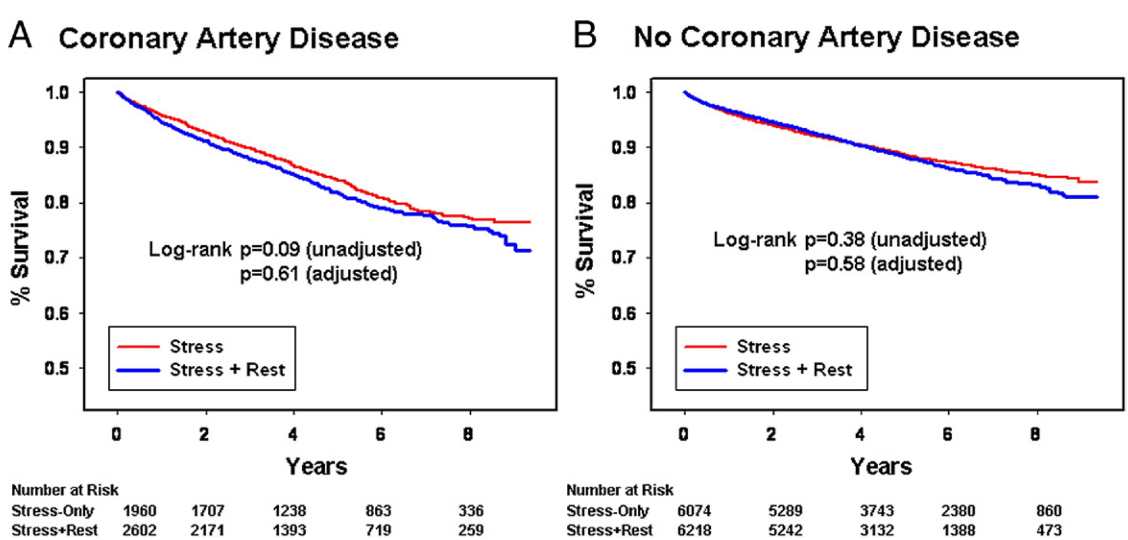

Figure 4 **Survival on the Basis of CAD Status for Each SPECT Protocol**

Survival curves on the basis of the presence **(A)** or absence **(B)** of coronary artery disease (CAD) for each single-photon emission computed tomographic myocardial perfusion imaging (SPECT) protocol. Patients with CAD had a higher mortality rate than non-CAD patients, irrespective of the imaging protocol used to evaluate them.

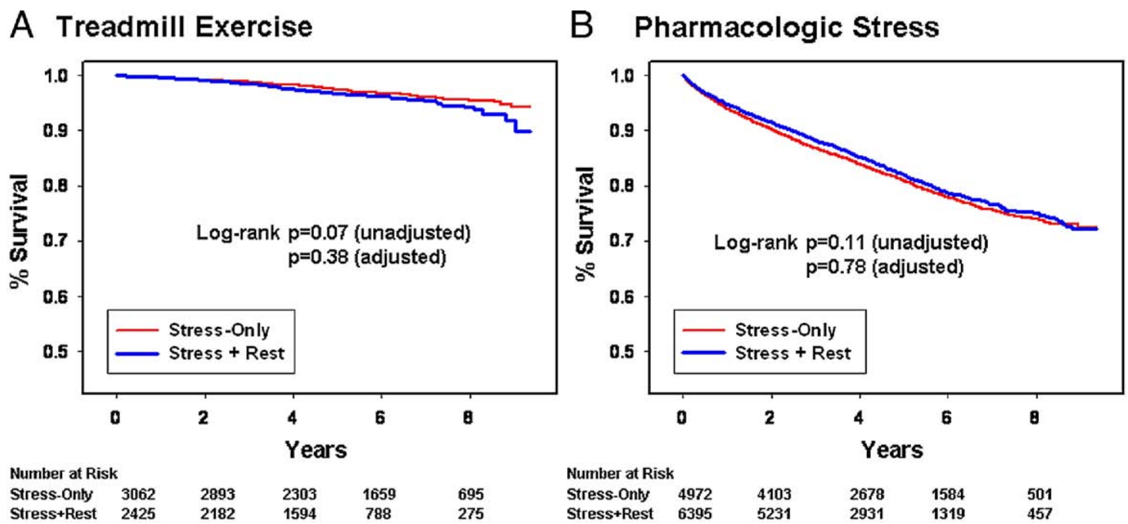

Figure 5 **Survival on the Basis of Stressor Modality for Each SPECT Protocol**

Survival curves on the basis of the stressor modality used for each single-photon emission computed tomographic myocardial perfusion imaging (SPECT) protocol. Patients undergoing treadmill exercise **(A)** had a significantly lower mortality than those who had pharmacologic stress testing **(B)**. However, within both groups, mortality rates were similar among the 2 imaging protocols.

Our patients had an all-cause annual mortality rate of 2.74%, which translates into an estimated cardiac mortality of 0.8%, assuming that 30% of all deaths are due to cardiac causes (16,17). Of note, 68% of our patients had pharmacologic stress testing rather than treadmill exercise. Patients undergoing pharmacologic stress are reported to have an annual cardiac mortality of 0.8%, as compared with 0.15% among those undergoing exercise stress (9). In our patients who exercised, the annual all-cause mortality was 0.6%, which translates into a comparable cardiac mortality of 0.18% with the aforementioned assumptions.

There are certain patient subgroups known to be at higher risk for death despite a normal SPECT result. A recent study reported a 2-fold higher annual cardiac mortality among diabetic (1.25%) versus nondiabetic (0.8%) patients (7). We also noted a 2-fold higher all-cause

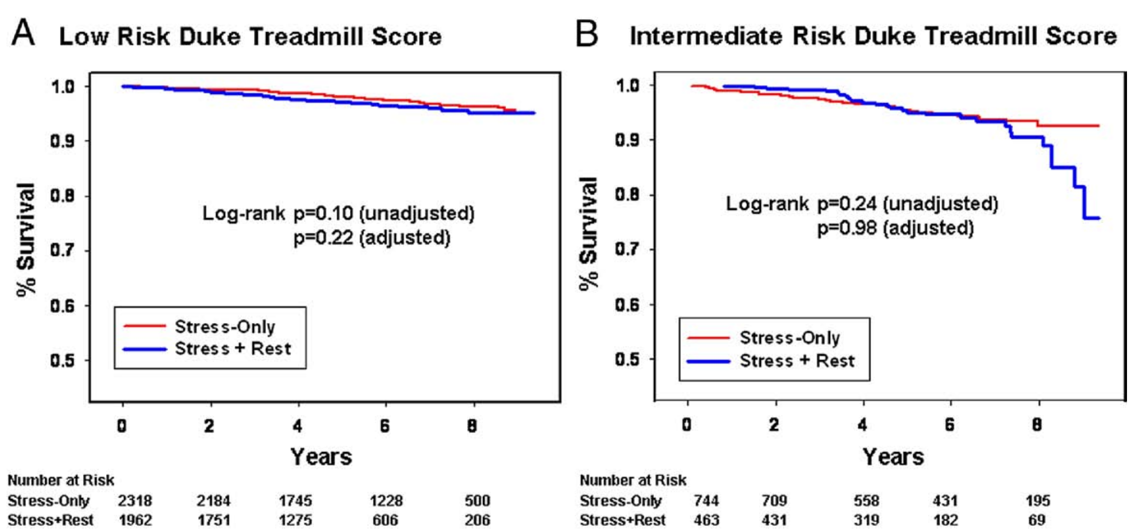

Figure 6 **Survival on the Basis of Duke Treadmill Score for Each SPECT Protocol**

Survival curves on the basis of a low **(A)** or intermediate **(B)** risk Duke treadmill score for each single-photon emission computed tomographic myocardial perfusion imaging (SPECT) protocol. Patients with a low-risk Duke treadmill score had a significantly lower mortality rate than those with an intermediate-risk score, irrespective of the imaging protocol they received.

Table 4 Univariate and Multivariable Predictors of Mortality

Predictor	Univariate TR	Univariate 95% CI	Univariate p Value	Multivariate TR	Multivariate 95% CI	Multivariate p Value
Increasing age	0.95	0.946–0.954	<0.001	0.962	0.958–0.966	<0.001
Male sex	0.90	0.81–1.00	0.06	0.667	0.597–0.745	<0.001
BMI <20 kg/m^2	0.39	0.27–0.57	<0.001	0.554	0.393–0.782	0.001
BMI 25–30 kg/m^2	1.70	1.47–1.95	<0.001	1.35	1.18–1.55	<0.001
BMI 30–35 kg/m^2	1.84	1.58–2.13	<0.001	1.42	1.23–1.65	<0.001
History of CAD	0.57	0.51–0.64	<0.001	0.774	0.689–0.871	<0.001
Dyspnea	0.43	0.29–0.69	<0.001	0.932	0.7768–1.12	0.459
Diabetes mellitus	0.41	0.37–0.46	<0.001	0.531	0.472–0.597	<0.001
Hypertension	0.50	0.44–0.56	<0.001	1.04	0.911–1.188	0.556
Smoking	0.52	0.45–0.61	<0.001	0.607	0.522–0.708	<0.001
Inpatient status	0.266	0.23–0.3	<0.001	0.519	0.462–0.583	<0.001
Pharmacologic stress	0.1	0.09–0.12	<0.001	0.207	0.172–0.25	<0.001
Chest pain	3.05	2.68–3.46	<0.001	2.04	1.80–2.31	<0.001
Hyperlipidemia	1.34	1.19–1.51	<0.001	1.88	1.67–2.133	<0.001
Exercise stress	1.87	1.49–2.37	<0.001	1.019	0.804–1.27	0.937
LVEF	1.00	0.97–1.01	0.43	1.001	0.995–1.007	0.685
Stress and rest imaging	0.89	0.80–0.99	0.03	1.008	0.906–1.12	0.887

CI = confidence interval; TR = time ratio; other abbreviations as in Table 1.

mortality in diabetic (4.5%) versus nondiabetic (2.1%) patients, which extrapolates to a cardiac death rate of 1.35% and 0.6%, respectively. Our patients with CAD also had, as in other trials, a significantly higher mortality rate (8). In this regard, the results we report are very consistent with mortality rates in the published data, in patients who have a normal SPECT.

Study limitations. Because this was a retrospective study, significant differences in baseline clinical characteristics were observed between patients in the 2 imaging protocols. However, raw mortality rates were consistently lower in the stress-only group and across all patient subgroups. Despite its retrospective design, this study evaluated a large, diverse, consecutive series of patients where the criteria for interpreting a study as normal were routinely used by 2 experienced nuclear cardiologists. Another limitation is that we do not have information on the cause of death or the frequency of other nonfatal cardiac events. However, on the basis of the similarity of our mortality rates with those reported in the published data, it is unlikely that our frequency of nonfatal myocardial infarction would have significantly differed from published results.

Conclusions

Patients determined to have a normal SPECT on the basis of stress imaging alone have a similar low mortality rate as those who undergo stress and rest imaging. Our results support that patients who have a normal-appearing initial stress SPECT do not require additional rest imaging. This imaging strategy will significantly reduce radiation exposure in a substantial number of patients.

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