Prediction of Death and Nonfatal Myocardial Infarction in High-Risk Patients: A Comparison Between the Duke Treadmill Score, Peak Exercise Radionuclide Angiography, and SPECT Perfusion Imaging

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Radionuclide exercise testing provides prognostic information in patients with known or suspected coronary artery disease (CAD). The relative contribution of 3 noninvasive tests—the Duke treadmill score (DTS), first-pass radionuclide angiography with calculation of the ejection fraction (RNA-EF), and perfusion SPECT—has not been comparatively assessed in a high-risk population undergoing all 3 tests. **Methods:** We identified 997 patients (75% male; median age, 60 y) who underwent exercise treadmill testing with RNA-EF and SPECT perfusion imaging as a single test. The relative prognostic power of each test was evaluated in both an unadjusted manner and after adjustment for differences in baseline characteristics using Cox proportional hazards models. **Results:** During a median follow-up of 4.1 y, 175 patients experienced outcome events. Without adjustment for baseline patient characteristics, each of the modalities proved highly predictive of the composite endpoint of cardiovascular death or nonfatal myocardial infarction (MI) (DTS χ^2 = 18.9, P = 0.0001; RNA-EF χ^2 = 34, P = 0.0001; SPECT χ^2 = 11.5, P = 0.0007). In clinically risk-adjusted models, RNA-EF was the most powerful predictor of cardiovascular death compared with the DTS and SPECT (χ^2 = 40.5, 27.6, and 19.8, respectively). Conversely, exercise SPECT perfusion was a stronger predictor of nonfatal MI than the DTS or RNA-EF (χ^2 = 26.7, 15.7, and 16.7, respectively). **Conclusion:** The DTS, perfusion SPECT, and RNA-EF are each significant predictors of cardiovascular events in high-risk patients. The optimal risk stratification of patients for CAD may include all 3 modalities.

Key Words: coronary disease; prognosis; nuclear medicine

J Nucl Med 2005; 46:5–11

Proper risk stratification is critical for the management of patients with known or suspected coronary artery disease (CAD). Informed choices regarding revascularization procedures or medical therapy can only be made after accurately identifying the patients who may benefit most with a given treatment strategy. Whereas exercise treadmill testing remains the cornerstone technique to achieve this purpose, noninvasive radionuclide exercise testing has been shown to reliably risk-stratify patients and to provide important prognostic information beyond that furnished by clinical variables and standard exercise testing (*1–11*).

Both first-pass radionuclide angiography with calculation of the ejection fraction (RNA-EF) and perfusion SPECT have demonstrated prognostic power in patients with known or suspected CAD (*6,10,12,13*). However, since the earliest descriptions of the combined technique of SPECT, RNA-EF, and exercise treadmill testing, there are few data on the prognostic power of this combination in a high-risk population (*12,14*). The purpose of our study was to examine the relative prognostic power of the Duke treadmill score (DTS), RNA-EF, perfusion SPECT, and clinical information in a high-risk population of patients with known or suspected CAD.

MATERIALS AND METHODS

We identified 1,055 patients who underwent both the Bruce protocol exercise treadmill testing with RNA-EF and SPECT perfusion imaging as a single test and diagnostic coronary angiography within 180 d (before or after) of stress testing at Duke University Medical Center between September 1993 and January 2002. After excluding patients with incomplete nuclear or baseline descriptor data, 997 patients with complete data were available for analysis.

Received Dec. 15, 2003; revision accepted May 21, 2004.

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Stress Testing

The study patients exercised using the standard Bruce protocol with 3-min stages. Whenever possible, cardiac medications (particularly β-blockers) were not administered for 48 h before exercise testing. The DTS was calculated as described by Mark et al. (*1*).

SPECT Myocardial Perfusion Imaging Protocol

The protocol for performing SPECT myocardial perfusion imaging studies at Duke University Medical Center has been previously described (*15*). In summary, SPECT data were obtained with multihead detectors by use of a step-and-shoot protocol. Rest images were obtained for 30 s per projection and stress images were obtained for 20 s per projection. A dual-isotope protocol was used for most patients with ^{201}Tl, the default agent for obtaining rest images. The usual ^{201}Tl dose was 148 MBq (4 mCi). ^{99m}Tc-Labeled perfusion agents were used for the stress portion of the examination. In patients who weighed >127 kg (>280 lb), ^{99m}Tc-labeled perfusion agents were used for the rest and stress portions of the examination. The usual ^{99m}Tc doses were 370 MBq (10 mCi) for rest and 1,110 MBq (30 mCi) for exercise.

Studies were independently reviewed and interpreted by specialists in nuclear medicine or nuclear cardiology. A 12-segment reporting system was used to quantify perfusion in various vascular territories, similar to methods previously described (*10,16,17*). The relative perfusion grade of each segment was quantified by visual assessment at rest and exercise with 4 gradations: 0 = no defect, 1 = mild defect, 2 = moderate defect, and 3 = severe defect. A cumulative summed stress score (SSS) was obtained by adding the scores of the 12 segments with exercise. Therefore, the SSS would equal 0 in a normal study, and the maximum score would be 36 (severe perfusion defect in all 12 segments). A summed rest score (SRS) was similarly calculated from the perfusion grades at rest. The summed difference score (SDS) was calculated from the differences in the SSS and SRS. The score variable has been previously shown to be highly predictive of cardiovascular outcomes using a 20-segment model (*9*).

First-Pass RNA-EF Study Protocol

First-pass RNA-EF studies were performed at peak stress using a previously described protocol (*18,19*). Briefly, first-pass studies were performed after administration of ^{99m}Tc-labeled perfusion agents through an external jugular or antecubital vein use of a multicrystal camera. Counts were obtained at 25-ms intervals for 30 s and motion correction was routinely performed.

Follow-Up and Statistical Analysis

Baseline clinical variables were collected prospectively at the time of catheterization and stored in the Duke Databank for Cardiovascular Disease. Discrete measures are reported as numbers and percentages, whereas continuous variables are reported as the median and the 25th and 75th percentiles. Data collection and follow-up in the Databank have been previously described (*6,20,21*). Briefly, patients were monitored by mailed questionnaires and telephone interviews at 6 mo, 1 y, and then annually. Patients were monitored for the outcomes of all-cause death, cardiovascular death, myocardial infarction (MI), and revascularization. An independent clinical events committee reviewed and classified all events without knowledge of the patient's clinical, catheterization, or nuclear results.

We evaluated the relative prognostic power of each test both in an unadjusted manner and after adjustment for baseline characteristics. Linearity assumptions were tested for all continuous and ordered categoric measures, and variables were transformed as needed to satisfy the assumption. For all endpoints (all-cause death, cardiovascular death, nonfatal MI, and composite cardiovascular death or nonfatal MI), we constructed models of the most important clinical predictors of outcome using a stepwise selection process from a list of candidate variables: age, sex, race, hypertension, vascular disease, modified Charlson comorbidity index (with history of MI and heart failure removed for consideration separately), history and severity of heart failure, ventricular gallop, carotid bruits, diabetes, prior revascularization, and prior MI (*22*). Models retained variables that were statistically significant at the $P < 0.05$ level. Each baseline hazard score incorporated variables in a composite index that, when inserted into a model, added 1 degree of freedom. Sequential Cox regression models were constructed for each endpoint, beginning with the baseline hazard and adding each test (DTS, RNA-EF, and SSS) until completion of full models containing all 4 predictors. For the models of cardiovascular death, patients were censored at the time of the last follow-up or the time of the noncardiac death. For the models of nonfatal MI, patients who did not experience this outcome were censored at either the time last known to be alive or death. Because of the likely impact of revascularization on outcomes, analyses were repeated in full, excluding patients who underwent revascularization within 60 d after stress testing. P values > 0.05 are reported as nonsignificant (NS).

RESULTS

Baseline characteristics for the study population are given in Table 1. In our group of 997 patients, the median age was 60 y. Of these patients, 599 (60%) underwent catheterization before nuclear testing and 268 (27%) were inpatients at the time of stress testing. A small minority of patients (4.7%) underwent stress testing within 60 d after MI. Approximately 75% were male and 89% were white. Prior revascularization had occurred in 67% and prior MI had been reported in 43%. During follow-up (median, 4.1 y), outcome events (death or nonfatal MI) occurred in 175 patients. There were 126 deaths (87 cardiovascular) and 59 nonfatal MIs. Of those who had a nonfatal MI, 10 patients subsequently experienced cardiovascular death at a later time. In the year after stress testing, 169 patients underwent coronary revascularization procedures (61 patients within 60 d). An additional 107 patients received revascularization after the first year of follow-up.

All-Cause Death

The models for all-cause death are shown in Table 2. In the unadjusted models, RNA-EF ($\chi^2 = 22.4$, $P = 0.0001$) and the DTS ($\chi^2 = 21.5$, $P = 0.0001$) were both significant predictors of survival. The baseline hazard score incorporating age, prior MI, prior percutaneous coronary intervention (PCI), diabetes, congestive heart failure (CHF) severity, vascular disease, ventricular gallop, and the modified Charlson index was also a significant predictor of survival ($\chi^2 = 21.3$, $P = 0.0001$). After adjustment for this hazard score, RNA-EF ($P = 0.0001$) and the DTS ($P = 0.0003$) remained significant independent predictors of all-cause

TABLE 1
Baseline Characteristics

Characteristic	CV death (n = 87)*	Nonfatal MI (n = 59)*	All patients (n = 997)
Median age† (y) [25th, 75th]	61 [51, 68]	63 [55, 71]	60 [52, 68]
Male‡	59 (68)	44 (75)	751 (75)
White‡	77 (89)	51 (86)	885 (89)
Diabetes‡	33 (38)	30 (51)	223 (22)
History of smoking‡	61 (70)	39 (66)	663 (66)
Hypertension‡	61 (70)	43 (73)	619 (62)
Peripheral vascular disease‡	11 (13)	14 (24)	118 (12)
Cerebrovascular disease‡	14 (16)	15 (25)	155 (16)
Carotid bruits‡	11 (13)	9 (15)	104 (10)
History of angina‡	73 (84)	54 (92)	860 (86)
CHF‡	47 (54)	19 (32)	328 (33)
NYHA class IV CHF‡	4 (5)	1 (2)	18 (2)
Previous PCI‡	30 (35)	26 (44)	363 (36)
Previous CABG‡	38 (44)	44 (75)	451 (45)
Prior MI‡	44 (51)	37 (63)	435 (44)
No. of diseased vessels‡			
0	18 (22)	3 (5)	284 (29)
1	17 (21)	11 (19)	217 (22)
2	25 (29)	14 (24)	195 (20)
3	23 (28)	31 (52)	280 (29)
Median SSS† (25th, 75th)	6 (0, 12)	7 (3, 10)	3 (0, 9)
Median DTS† (25th, 75th)	3 (0, 4.5)	2.6 (−1.5, 4.4)	4 (0, 6)
Median first-pass RNA-EF† (25th, 75th)	44 (33, 56)	55 (39, 61)	56 (45, 65)

*Ten nonfatal MI patients also experienced cardiovascular (CV) death at later date.
†Median with 25th and 75th percentiles in brackets or parentheses.
‡Median with percentage in parentheses.
CHF = congestive heart failure; PCI = percutaneous coronary intervention; CABG = coronary artery bypass graft.

death. None of the perfusion scores was an important predictor for all-cause death.

In the series of incremental models, addition of RNA-EF to the combination of the baseline hazard and DTS significantly improved the predictive power of the model (with or without SSS, all $P < 0.0005$). In the full model, the baseline hazard ($P = 0.0036$), DTS ($P = 0.008$), and RNA-EF ($P = 0.0001$) were all important predictors for all-cause death (Table 3).

TABLE 2
Models for All-Cause Death

Parameter	Unadjusted		Adjusted for baseline hazard score	
	Model χ^2	Model P value	Model χ^2	Incremental P value*
RNA-EF	22.4	0.0001	36.4	0.0001
DTS	21.5	0.0001	34.3	0.0003
SSS	2.2	NS	22.4	NS
SRS	3.1	NS	23.0	NS
SDS	0.032	NS	21.3	NS
Baseline hazard score	21.3	0.0001		

*For addition to baseline hazard score.
NS = not significant.

Cardiovascular Death

The models for cardiovascular death are shown in Table 4. RNA-EF ($\chi^2 = 34.5$, $P = 0.0001$), DTS ($\chi^2 = 19.9$, $P = 0.0001$), SSS ($\chi^2 = 8.1$, $P = 0.0044$), and SRS ($\chi^2 = 8.3$, $P = 0.0041$) were all significant predictors of survival in the unadjusted models. After adjustment for the baseline hazard score (incorporating age, prior MI, prior PCI, diabetes, CHF, CHF severity, vascular disease, white race, and the modified Charlson index), these same 4 variables remained significant independent predictors of cardiovascular death. The SDS was not an important predictor for cardiovascular death.

As seen with all-cause death, inclusion of RNA-EF in the incremental regression models improved the predictive power of the model (all $P < 0.0001$). Data from the complete model for cardiovascular death are shown in Table 3. In this full model, only RNA-EF ($P = 0.0001$) and the DTS ($P = 0.014$) were independent predictors of cardiovascular death. The SSS did not predict cardiovascular death.

Nonfatal MI

Data from the models for nonfatal MI are shown in Table 5. RNA-EF ($\chi^2 = 6.2$, $P = 0.0126$) and the SSS ($\chi^2 = 14.8$,

TABLE 3
Complete Models for All Endpoints

Endpoint	Variable	All patients (n = 997)		Without early revascularization (n = 936)	
		Wald χ^2	P value	Wald χ^2	P value
All-cause death	Baseline hazard	8.5	0.0036	7.9	0.0049
	DTS	7.0	0.0080	6.8	0.0089
	RNA-EF	15.7	0.0001	16.4	0.0001
	SSS	2.8	NS	3.2	NS
CV death	Baseline hazard	3.1	NS	3.0	NS
	DTS	6.0	0.014	5.8	0.016
	RNA-EF	19.0	0.0001	18.2	0.0001
	SSS	0.8	NS	0.9	NS
Nonfatal MI	Baseline hazard	11.2	0.0008	4.2	0.039
	DTS	1.0	NS	0.3	NS
	RNA-EF	0.3	NS	2.2	NS
	SSS*	9.2	0.0101	0.0	NS
CV death or nonfatal MI	Baseline hazard	10.8	0.0010	6.0	0.014
	DTS	6.1	0.014	4.6	0.03
	RNA-EF	14.5	0.0001	17.9	0.0001
	SSS	0.2	NS	0.8	NS

*SSS included as 2 variables to meet linearity-in-hazard assumption for Cox model.
NS = not significant; CV = cardiovascular.

P = 0.0006) were significant predictors of survival in the unadjusted models. After adjustment for the baseline hazard score (incorporating modified Charlson index, CHF severity, hypertension, diabetes, carotid bruits, prior PCI, prior MI, age, and white race), only the SSS (P = 0.0003) remained a significant predictor of nonfatal MI. The DTS and other perfusion scores were not predictive of MI in any models.

In the sequential models, only the SSS added significant predictive power ($P < 0.005$). Neither RNA-EF nor the DTS appeared to add incremental information to the baseline hazard. Besides the baseline hazard score (P = 0.008), the SSS (P = 0.01) was also the only significant predictor for nonfatal MI in the complete model (Table 3). As seen in the sequential models, neither RNA-EF nor the DTS appeared to add any prognostic information for this endpoint in the full model.

Cardiovascular Death or Nonfatal MI

The models for this composite endpoint are shown in Table 6. RNA-EF (χ^2 = 34.0, P = 0.0001), DTS (χ^2 = 18.9, P = 0.0001), SSS (χ^2 = 11.5, P = 0.0007), and SRS (χ^2 = 10.3, P = 0.0013) were all predictors of the composite endpoint in the unadjusted models. After adjustment for the baseline hazard score (incorporating modified Charlson index, CHF severity, diabetes, prior PCI, carotid bruits, hypertension, prior MI, age, and white race), RNA-EF (P = 0.0001), DTS (P = 0.0009), SSS (P = 0.0073), and SRS

TABLE 4
Models for Cardiovascular Death

Parameter	Unadjusted		Adjusted for baseline hazard score	
	Model χ^2	Model P value	Model χ^2	Incremental P value*
RNA-EF	34.5	0.0001	40.5	0.0001
DTS	19.9	0.0001	27.6	0.0002
SSS	8.1	0.0044	19.8	0.0151
SRS	8.3	0.0041	19.7	0.0160
SDS	0.3	NS	14.2	NS
Baseline hazard score	13.9	0.0001		

*For addition to baseline hazard score.
NS = not significant.

TABLE 5
Models for Nonfatal MI

Parameter	Unadjusted		Adjusted for baseline hazard score	
	Model χ^2	Model P value	Model χ^2	Incremental P value*
RNA-EF	6.2	0.0126	16.7	NS
DTS	3.1	NS	15.7	NS
SSS	14.8	0.0006	26.7	0.0003
SRS	2.2	NS	14.4	NS
SDS	3.2	NS	17.0	NS
Baseline hazard score	13.6	0.0001		

*For addition to baseline hazard score.
NS = not significant.

TABLE 6
Models for Cardiovascular Death or Nonfatal MI

Parameter	Unadjusted		Adjusted for baseline hazard score	
	Model χ^2	Model *P* value	Model χ^2	Incremental *P* value*
RNA-EF	34.0	0.0001	48.4	0.0001
DTS	18.9	0.0001	35.6	0.0009
SSS	11.5	0.0007	31.8	0.0073
SRS	10.3	0.0013	30.4	0.0160
SDS	1.1	NS	25.9	NS
Baseline hazard score	24.6	0.0001		

*For addition to baseline hazard score.
NS = not significant.

($P = 0.0160$) all remained significant independent predictors for cardiovascular death or nonfatal MI.

In the sequential models for cardiovascular death or nonfatal MI, each of the 3 testing variables (RNA-EF, DTS, SSS) added predictive power (all $P < 0.05$). In the full model for the combination of cardiovascular death or nonfatal MI, the baseline hazard ($P = 0.001$), DTS ($P = 0.01$), and RNA-EF ($P = 0.0001$) were each important predictors for events (Table 3).

Impact of Revascularization

Because revascularization would be expected to change the SSS and alter the "natural" history of coronary disease, inclusion of these patients might have decreased the predictive power of SPECT perfusion imaging. However, repeating the analyses after exclusion of patients who underwent early revascularization (within 60 d after stress testing) did not substantively alter our results. Data for the full models of all endpoints in this population are shown in Table 3.

DISCUSSION

Exercise treadmill testing, perfusion SPECT, and RNA-EF have all demonstrated significant predictive power for cardiovascular events. With attention to 4 endpoints (all-cause death, cardiovascular death, nonfatal MI, and cardiovascular death or nonfatal MI), our study demonstrates the complementary prognostic power of RNA-EF, the DTS, and SPECT perfusion. Even in combination with the baseline clinical hazard, each of these techniques offers additional predictive information for a major cardiovascular event. Both the DTS and RNA-EF were potent predictors for all-cause death and cardiovascular death. In contrast, SPECT perfusion was the most powerful predictor for nonfatal MI. All 3 techniques were important predictors of the combined endpoint of cardiovascular death or nonfatal MI.

Previous Work

These findings are consistent with and build on the results of previous investigators. Exercise treadmill testing has long been the cornerstone of noninvasive risk stratification. Mark et al. demonstrated that a treadmill score incorporating exercise time, ST segment changes, and angina was a powerful predictor of survival in both inpatients and outpatients (*1,23*). For outpatients, those with a low-risk DTS had a 99% 4-y survival compared with a 79% survival rate for patients with a high-risk score (*23*). The DTS maintains prognostic power even in models that incorporate clinical characteristics (*4,23*). Despite the utility of the DTS as a prognostic tool, other investigators have shown that radionuclide imaging techniques offer complementary prognostic information for patient management. These techniques have been particularly helpful in prognosis for nonfatal events (MI, revascularization)—endpoints for which the DTS, configured for cardiovascular death, was not designed to predict (*1*). In this cohort (median DTS, 4), we would have expected a survival rate between those observed for intermediate- and low-risk DTS cohorts. Our observed event rate (12.6% mortality over the median 4.1-y follow-up) was actually much higher, demonstrating that this selected population was at higher risk than the DTS alone would suggest and that other data, such as perfusion imaging, improve risk prediction.

Gibbons et al. examined 4,649 patients who underwent exercise testing and had both intermediate-risk DTS and normal or near-normal SPECT perfusion studies (*7*). In this group, cardiac survival at 5 y was 99%, leading the authors to conclude that even with an intermediate-risk DTS, a low-risk perfusion study identified patients at low risk for cardiac events (*7*). Similarly, Hachamovitch et al. found, in a cohort of 2,200 patients, SPECT perfusion results stratified patients at each level of the DTS into distinct risk groups for cardiovascular events ($P < 0.05$) (*24*). In a cohort of 388 patients with high exercise tolerance (Bruce stage IV or greater), Chatziioannou et al. found that although the DTS alone contained no prognostic power for cardiac events, SPECT perfusion scores were highly predictive for the same endpoint (*8*). Because a large part of the predictive power for the DTS comes from the exercise duration, selecting only patients with high exercise tolerance limited the utility of the DTS. These studies verified that SPECT perfusion imaging may add important information for the risk stratification of patients within the DTS subgroups.

EF assessments from both RNA-EF and gated myocardial perfusion SPECT have been shown to predict events in patients with documented coronary disease (*3,10,24–27*). These parameters appear to add to clinical and treadmill variables, though no large studies have specifically addressed the incremental value of exercise EF to the DTS (*3,28*). In a study population of 571 patients, Lee et al. found that exercise EF contributed 59% of the prognostic information in a model that also included coronary anatomy (number of diseased vessels), age, and other clinical and exercise variables (*3*).

Prior comparisons of EF assessment techniques with SPECT perfusion imaging suggest different prognostic applications. As we found in our study, EF has been shown to be a more powerful predictor for survival, whereas perfusion is a more powerful predictor for nonfatal MI. In their cohort of 2,686 patients, Sharir et al. found that the single best predictor for cardiovascular death was EF and the single best predictor for MI was perfusion (*16*). Similarly, in their survey of SPECT studies, Iskander and Iskandrian found that reversible perfusion defects were an important predictor of nonfatal MI (*5*). Though perfusion's relationship to MI is presumably rooted in the amount of myocardium in jeopardy, there is no definite pathophysiologic explanation for these findings. Nevertheless, because as many as 50% of events in patients with preserved EF may be nonfatal MI, accurate risk stratification for these events remains a major clinical concern (*29*).

Though exercise treadmill testing, RNA-EF, and SPECT perfusion imaging have each been shown to have predictive power for cardiovascular events, there are few data regarding the prognostic power of these techniques in combination (*12*). Although Palmas et al. have shown the advantages of combining techniques for identifying the extent of CAD, this study is the first to examine the relative contributions of these variables to the long-term prognosis of a large cohort of patients for an array of endpoints (*14*).

Limitations

This study had several limitations. First, these data represent the experience from one academic medical center in patients who all underwent cardiac catheterization. Because this cohort comprises a selected high-risk group and our findings have not been tested in another sample, our results should be applied cautiously to dissimilar patient populations. Second, because our database supported only 12 segments at the outset of the data collection period, this study used a 12-segment perfusion model. Currently, the American Society of Nuclear Cardiology recommends a 17- or 20-segment system (*30*). In addition, a 5-step scoring system is recommended for the grading of perfusion, and our system used only a 4-grade scale. Although the recommended model would provide greater ability to define regions of defect within the myocardium, and may provide a higher resolution of the SSS, the 2 systems are qualitatively analogous when a perfusion defect is present. Third, we chose exercise rather than resting EF as the radionuclide angiography variable. Although most centers assess left ventricular function by poststress gated SPECT, exercise EF has been shown to have a higher predictive power for both death and cardiovascular events (*3,25,26*). Therefore, we elected to use exercise EF in our models. Unfortunately, our analysis set lacked the consistent measurement of EF by gated SPECT necessary for a direct comparison of the 2 techniques, but substantial literature documents the prognostic use of resting EF by gated SPECT and supports its use as an alternative method (*10,16,24,27*). Finally, analysis of nonfatal MI as a separate endpoint can be problematic and is generally discouraged in the clinical trials setting (*31*). Although we have included this as a separate endpoint for completeness, these results should be viewed in the larger context of its combination with other endpoints.

CONCLUSION

The DTS, perfusion SPECT, and RNA-EF are each significant predictors of cardiovascular events in high-risk patients. Though RNA-EF is the strongest predictor of cardiovascular and all-cause mortality, SPECT perfusion imaging most powerfully predicts nonfatal MI and the composite endpoint of cardiovascular death, nonfatal MI, and revascularization. Because of the complementary nature of these techniques, the optimal risk stratification of high-risk patients for CAD may include the combined assessment of left ventricular function and perfusion.

ACKNOWLEDGMENT

This work was presented in abstract form at the 7th Annual Symposium and Scientific Session, American Society of Nuclear Cardiology, September 26–29, 2002, Baltimore, MD.

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