Incremental Prognostic Value of Post-Stress Left Ventricular Ejection Fraction and Volume by Gated Myocardial Perfusion Single Photon Emission Computed Tomography

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Background—The incremental prognostic value of post-stress left ventricular ejection fraction (EF) and volume over perfusion has not been investigated.

Methods and Results—We identified 1680 consecutive patients who underwent rest Tl-201/stress Tc-99m sestamibi gated single photon emission computed tomography (SPECT) and who were followed-up for 569 ± 106 days. Receiver-operator characteristics analysis defined an EF$<$45%, an end-systolic volume (ESV) $>$70 mL, and an end-diastolic volume $>$120 mL as optimal thresholds, yielding moderate sensitivity and high specificity in the prediction of cardiac death. Patients with an EF$\geq$45% had mortality rates $<$1%/year, despite severe perfusion abnormalities, whereas patients with an EF$<$45% had high mortality rates, even with only mild/moderate perfusion abnormalities (9.2%/year; $P<0.00001$). Similarly, an ESV$\leq$70 mL was related to a low cardiac death rate ($<$1.2%/year), even for patients with severe perfusion abnormalities, whereas patients with an ESV$>$70 mL and only mild/moderate perfusion abnormalities had high death rates (8.2%/year; $P<0.00001$). Patients with an EF$<$45% and an ESV$\leq$70 mL had low cardiac death rates (1.7%/year); those with an EF$<$45% but an ESV$>$70 mL had high death rates (7.9%/year; $P<0.02$). Multivariate Cox proportional hazards regression showed that perfusion variables and ESV were independent predictors of overall coronary events, whereas EF and ESV demonstrated incremental prognostic values over prescan and perfusion information in predicting cardiac death and cardiac death or myocardial infarction.

Conclusions—Post-stress EF and ESV by gated-SPECT have incremental prognostic values over prescan and perfusion information in predicting cardiac death, and they provide clinically useful risk stratification. (***Circulation***. 1999;100:1035-1042.)

Key Words: myocardial perfusion ■ imaging ■ cardiac volume ■ prognosis

Identifying patients at risk for cardiac events is the primary objective of the noninvasive evaluation of patients with known or suspected coronary artery disease (CAD). Previous studies demonstrated the incremental prognostic value of myocardial perfusion single photon emission computed tomography (SPECT), over clinical and exercise data, in predicting cardiac death and nonfatal myocardial infarction (MI).[1–5] The value of left ventricular function in risk assessment has also been well documented, particularly in identifying patients at increased risk of cardiac death.[6–8] These studies showed that rest or exercise left-ventricular ejection fraction (EF) was a major determinant of long-term survival in patients with CAD. The prognostic value of left ventricular volume has been less extensively evaluated due to technical difficulties and inaccuracy in its measurement. However,

end-systolic volume (ESV) has been shown as an independent predictor of cardiac death in patients after MI and coronary artery bypass surgery.[9,10]

The addition of gating to routine myocardial perfusion SPECT provides accurate and reproducible information on left ventricular function[11,12] and volume.[13] Early post-stress acquisition of gated SPECT, after the injection of Tc-99m sestamibi at peak stress, provides information regarding peak stress perfusion and myocardial function at the time of acquisition.[12,14] The incremental prognostic value of post-stress left ventricular function and volume measurements over perfusion parameters has not been evaluated.

The goal of the present study was to evaluate whether post-stress EF and left ventricular volume, measured by gated myocardial perfusion SPECT, had incremental prognostic value over clinical,

exercise, and perfusion data in predicting cardiac death in a large, unselected population of patients referred for nuclear testing.

Methods

Study Population

We identified 1924 consecutive patients who underwent separate acquisition dual-isotope myocardial-perfusion gated SPECT (rest Tl-201/stress Tc-99m sestamibi gated SPECT) at Cedars-Sinai Medical Center and who were followed-up ≥1 year for cardiac events. Patients with nonischemic cardiomyopathy (EF<45% and prescan likelihood of CAD<0.40) were excluded (n=15), and patients revascularized within 60 days after nuclear testing (n=229) were censored from the prognostic portion of the analysis,[15,16] which left 1680 patients (1029 underwent treadmill exercise and 651 adenosine stress testing).

Normal limits of post-stress left ventricular volume and EF were determined in 44 patients (22 men and 22 women aged 53±10 years) with a low prescan likelihood (<5%) of CAD.[17]

Acquisition Protocol

All patients underwent separate dual-isotope myocardial perfusion SPECT as previously described.[18] Tl-201 (3 to 4.5 mCi) was injected intravenously at rest, and SPECT imaging was initiated 10 minutes later. Tc-99m sestamibi (25 to 40 mCi) was then injected during stress, and 8-frame gated SPECT imaging (100% acceptance window) was initiated 15 to 30 minutes after exercise or 30 to 60 minutes after adenosine stress. Acquisitions were performed using a 2-detector (Vertex, ADAC), 3-detector (Prism, Picker), or single detector (Orbiter, Siemens) camera to get 60 to 64 projections over 180° for 35 (Tl-201) or 25 seconds (Tc-99m sestamibi) per projection. The 8 projection sets were also summed to generate an "ungated" set. Projection images were filtered using a 2D Butterworth filter, order of 5 (Tl-201) or 2.5 (Tc-99m sestamibi), and a cutoff frequency of 0.25 cycles/pixel (Tl-201) or 0.3 cycles/pixel (Tc-99m); images were reconstructed into transaxial images using filtered backprojection with a ramp filter. No scatter or attenuation correction was applied.

Exercise Protocol

Patients were instructed to discontinue β-blockers and calcium antagonists 48 hours before testing and nitrates 6 hours before testing whenever possible. A symptom-limited treadmill exercise test (Bruce protocol) was performed. Patients received an injection of Tc-99m sestamibi at peak stress; they then exercised at the same level for an additional 60 seconds and for 2 minutes more at 1 level lower. Horizontal or downsloping ST segment depression ≥1 mm or upsloping ≥1.5 mm at 80 ms after the J point was considered positive. Failure to achieve 85% of maximal predicted heart rate or ischemic ECG response during exercise was followed by conversion to an adenosine stress test.

Adenosine Protocol

Patients were instructed to discontinue caffeine-containing products for 24 hours before the test. Adenosine (140 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was infused over 6 minutes, and Tc-99m sestamibi was injected at the end of the third minute. Whenever possible, patients performed a low-level treadmill exercise during the adenosine infusion.[19] ECG response was evaluated by the same criteria mentioned for exercise testing.

Visual Analysis of Perfusion SPECT

Perfusion images were scored semiquantitatively using a 20-segment, 5-point (0=normal uptake, 1=mildly reduced uptake, 2=moderately reduced uptake, 3=severely reduced uptake, and 4=no uptake) model for the left ventricle.[18] Summed stress score (SSS) and summed rest score (SRS) were calculated by adding the scores of 20 segments in the stress and rest images, respectively. Summed difference score (SDS) was derived as the difference between stress and rest scores. SSS<4 was considered normal,

SSS=4 to 13, mildly/moderately abnormal, and >13, severely abnormal.[5]

Quantitative Analysis of Gated Tc-99m Sestamibi SPECT

After automatic reorientation,[20] gated short-axis images were processed using the quantitative gated SPECT algorithm,[11] and left ventricular end-diastolic volume (EDV), ESV, and EF were automatically calculated.

Patient Follow-up

Patient follow-up consisted of scripted and blinded telephone interviews corroborated by objective methods.[3] The mean follow-up interval was 569±106 days (range, 365 to 968 days).

Prescan Likelihood of Coronary Artery Disease

Prescan likelihood of CAD was calculated using CADENZA,[17] which was based on a Bayesian analysis of prescan patient data. For patients undergoing exercise testing, the prescan likelihood of CAD included clinical history and exercise information, whereas for patients undergoing pharmacological stress testing, prescan likelihood was based on historical data only.

Statistical Analysis

Comparisons between patient groups were performed using 1-way ANOVA for continuous variables and the χ^2 test for categorical variables. Continuous variables were described by mean±SD. A value of $P<0.05$ was considered statistically significant.

Cox proportional hazards regression analysis was applied to determine the independent predictors of cardiac death, cardiac death or MI, and overall cardiac events (cardiac death, MI, or late revascularization) as separate end points. The variables tested were prescan likelihood of CAD; prior MI, coronary angioplasty, and/or coronary artery bypass surgery; type of stress; perfusion variables (SSS, SRS, and SDS); and gated SPECT variables (EF, EDV, and ESV). A value of $P<0.05$ in univariate analysis was required for inclusion in the multivariate analysis. Multivariate analysis was performed in a stepwise fashion, evaluating prescan, perfusion, and function data. At each step, variables were removed from the model, until all remaining variables were significantly independent ($P<0.05$).

Receiver-operator characteristics (ROC) analysis was performed to define thresholds for EF, EDV, and ESV; this analysis provided optimal sensitivity and specificity in predicting cardiac death. Thresholds were obtained by minimizing the expression $(1-\text{sensitivity})^2 + (1-\text{specificity})^2$.

Kaplan-Meier cumulative survival analysis with stratification by EF and ESV was performed, and survival curves were compared by the Wilcoxon test. Statistical significance was defined as $P<0.05$.

Results

Outcome Events

During the follow-up period, 156 coronary events (9.5%) occurred. These included 39 cardiac deaths (2.3%), 16 MIs (0.95%), and 101 late (>60 days) coronary revascularizations (6.0%)[15,16]; the latter category included 38 bypass surgeries (2.3%) and 63 coronary angioplasties (3.8%).

Patient Characteristics

Of the 1680 patients included in the prognostic analysis, 480 (25%) had a history of MI, 305 (18%) had a prior coronary angioplasty, and 336 (20%) had prior bypass surgery. Compared with patients with no cardiac events (Table 1), patients experiencing cardiac death and those experiencing cardiac death or MI were older and had a higher prescan likelihood of CAD; frequently had a history of MI and coronary angio-

TABLE 1. Patient Characteristics

	Cardiac Death (n=39)	Cardiac Death or MI (n=55)	Late Revascularization (n=101)	Early Revascularization (n=229)	No Event (n=1541)
Age	76±8†	74±9†	69±10†*	69±10	64±12
Male, n (%)	24 (62)	37 (67)	82 (81)†	170 (74)	1034 (61)
Hx of MI, n (%)	24 (62)†	31 (56)†	44 (44)†*	74 (32)	418 (25)
Hx of angioplasty, n (%)	13 (33)†	41 (75)†	39 (39)†	66 (29)	305 (18)
Hx of bypass surgery, n (%)	12 (31)	18 (33)	30 (30)	49 (21)	336 (20)
Exercise, n (%)	13 (33)†	15 (25)†	59 (58)†*	126 (55)	1060 (63)
Prescan likelihood of CAD	0.45±0.23†	0.48±0.27†	0.54±0.30†*	0.60±0.30†	0.39±0.31
SSS	16±11†	16±12†	12±9†*	18±10†	7±9
SRS	9±10†	8±10†	3±6*	3±5	2±6
SDS	7±6†	8±8†	8±7†	15±9†	4±6
EF, %	38±20†	41±19†	52±15†*	49±14†	58±15
EDV, mL	170±94†	148±90†	108±60†*	109±52†	93±64
ESV, mL	119±84†	100±80†	58±52†*	59±43†	44±43

Hx indicates history.
*$P<0.05$ vs cardiac death.
†$P<0.05$ vs no event.

plasty; and had higher SSS, SRS, and SDS values, lower EF, and higher ESV and EDV. Patients who had late revascularizations had higher SSS and SDS values, lower EF, and higher left ventricular volumes compared with patients with no events. However, compared with patients experiencing cardiac death, these patients had less severe perfusion abnormalities and better cardiac function. Patients who underwent early revascularization had higher SSS and SRS values, lower EF, and larger volumes compared with patients with no events. However, compared with patients who experienced cardiac death, these patients had better cardiac function.

Compared with patients who underwent exercise stress testing, those undergoing adenosine stress testing were older, more frequently had a history of MI or bypass surgery, and had a higher likelihood of CAD, more severe and extensive perfusion defects, worse cardiac function, and a higher frequency of cardiac death (Table 2).

Cox Proportional Hazards Regression for Prediction of Cardiac Events

The final models of multivariate analysis for prediction of cardiac death, cardiac death or MI, and cardiac death, MI, or late revascularization are summarized in Table 3. The independent variables for prediction of cardiac death were EF, ESV, and type of stress used; for prediction of cardiac death or MI, the variables were EF and ESV. The independent predictors of cardiac death, MI, or late revascularization were prescan likelihood of CAD, history of MI, type of stress, SSS and SRS, and ESV. The addition of EF and ESV to perfusion data resulted in a significant improvement in global χ^2 in the prediction of cardiac death compared with the model that contained perfusion data only ($\chi^2=72.13$ versus 31.1, respectively; $P<0.0001$).

Normal Values of EF, ESV, and EDV and Thresholds for Prediction of Cardiac Death

Table 4 summarizes the results of normal values of EF, ESV, and EDV in the 44 patients with <5% likelihood of CAD and

the results of ROC analysis for the prediction of cardiac death in the 1680 patients included in the prognostic evaluation. Based on ROC curves, optimal thresholds for the prediction of cardiac death were EF<45%, ESV>70 mL, and EDV>120 mL (−2.2, 2.9, and 2.0 SDs from the mean normal values, respectively). These thresholds yielded moderate sensitivities and high specificities for the prediction of cardiac death, and they were used in risk stratification in the following analyses.

TABLE 2. Patient Characteristics by Type of Stress

	Exercise Stress (n=1060)	Adenosine (n=620)
Age	64±12	71±11*
Male sex, n (%)	689 (67)	345 (53)*
Hx of MI, n (%)	204 (20)	214 (33)*
Hx of angioplasty, n (%)	190 (19)	115 (18)
Hx of bypass surgery, n (%)	176 (17)	160 (25)*
Prescan likelihood of CAD	0.34±0.34	0.47±0.21*
β-Blockers, n (%)	86 (8.3)	77 (11.8)
Nitrates, n (%)	44 (4.3)	58 (8.9)
Calcium-channel blockers, n (%)	107 (10.4)	90 (13.8)
%Max HR	92±9	NA
SSS	5.2±8.4	8.7±10.1*
SRS	1.6±5.1	3.7±7.6*
SDS	3.5±5.9	4.9±6.4*
EF, %	61±13	54±17*
EDV, mL	88±64	102±64*
ESV, mL	38±33	55±54*
Cardiac death, n (%)	8 (0.8)	31 (4.8)*
MI, n (%)	12 (1.17)	4 (0.6)

Hx indicates history; %Max HR, percent of maximum predicted heart rate; and NA, not applicable.
*$P<0.001$.

TABLE 3.   Final Multivariate Models for the Prediction of Cardiac Events

	Cardiac Death		Cardiac Death or MI		Cardiac Death, MI, or Late Revascularization	
	Wald χ^2	P	Wald χ^2	P	Wald χ^2	P
Hx of MI	...	NS	...	NS	8.76	0.003
Likelihood of CAD	...	NS	...	NS	11.36	0.0007
Type of stress	8.29	0.004	...	NS	4.04	0.044
SSS	...	NS	...	NS	18.23	0.00002
SRS	...	NS	...	NS	11.97	0.0005
EF	9.0	0.004	11.97	0.0005	...	NS
ESV	5.11	0.024	4.6	0.03	15.52	0.00008

Hx indicates history.

Figure 1. Cardiac death rate (%/year) as a function of perfusion abnormality and EF. The number of patients within each category is indicated below each column. Mod indicates moderate, and ABNL, abnormality.

EF and Cardiac Death

The annual cardiac death rate increased with the amount of perfusion abnormality. Normal perfusion (SSS≤3) was related to a very low mortality rate (0.3%/year), whereas mild/moderate and severe perfusion abnormalities (SSS=4 to 13 and >13, respectively) resulted in higher mortality rates (2.4%/year and 3.7%/year, respectively; $P<0.0001$ versus normal perfusion). Further stratification of these groups by EF (Figure 1) demonstrated that patients with an EF<45% and mild/moderate or severe perfusion abnormalities had high mortality rates (9.2% and 5.7%, respectively), whereas patients with an EF≥45% had a cardiac death rate <1%/year, regardless of the degree of perfusion abnormality. EF<45% was not related to a higher cardiac death rate in patients with normal perfusion.

ESV and Cardiac Death

Figure 2 illustrates cardiac death rate as a function of perfusion abnormality and ESV. An ESV≤70 mL was related to a low mortality rate, even in patients with severe perfusion abnormalities (0.4%/year), whereas an ESV>70 mL was related to a high death rate in patients with mild/moderate or severe perfusion abnormalities (8.2%/year and 7.5%/year, respectively; $P<0.00001$ versus ESV≤70 mL in the same perfusion category). Patients with normal perfusion had low (<1%/year) death rates, regardless of their ESV.

Incremental Value of ESV over EF

Multivariate analysis showed that ESV was an independent predictor of cardiac death after adjustment for EF (Table 3). The incremental prognostic value of ESV over EF is demon-
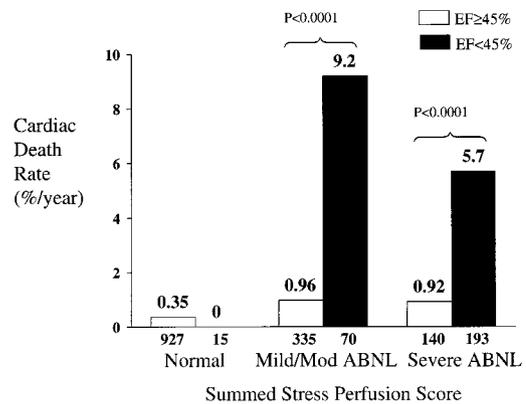
strated in Figure 3. An ESV>70 mL identified patients at a significantly higher risk than patients with a similar EF but an ESV≤70 mL. Patients with an EF<45% and an ESV>70 mL had a high cardiac death rate (7.9%/year), compared with a death rate of only 1.7%/year for patients with an EF<45% but an ESV≤70 mL ($P<0.017$). Even in patients with preserved global left ventricular function (EF≥45%), those with an ESV>70 mL had a relatively high death rate (2.6% versus 0.5%; $P<0.02$).

Exercise Versus Adenosine Stress

Figure 4 shows cardiac mortality rates in patients undergoing exercise and pharmacologic stress as a function of EF (Figure 4A) and ESV (Figure 4B). Patients with an EF<45% or an ESV>70 mL had significantly higher cardiac death rates, both in the exercise and the adenosine groups. Patients who underwent adenosine stress had higher mortality rates compared with patients undergoing exercise.

Kaplan-Meier Survival Analysis: Stratification by EF and ESV

Figures 5 and 6 show cumulative survival curves in patients with mild/moderate perfusion abnormalities and those with severe perfusion abnormalities, stratified by EF (Figure 5) and ESV (Figure 6). An EF≥45% and an ESV≤70 mL identified patients with low risk, even in the severe perfusion abnormality category. Patients with an EF<45% or with an ESV>70 mL were at a high risk for cardiac death. Cumulative survival curves of patients with an EF≥45% and an

TABLE 4.   Normal Values of EF, ESV, and EDV and ROC Analysis

	Normal Values (n=44)*		ROC Analysis (n=1680)†					
	Mean	SD	Threshold	#SD	Sensitivity	Specificity	Area	P
EF	62%	8%	45%	−2.2	69%	85%	0.81	0.000001
ESV	30 mL	14 mL	70 mL	2.9	69%	86%	0.79	0.000001
EDV	78 mL	21 mL	120 mL	2.0	69%	82%	0.77	0.000001

#SD indicates number of standard deviations from the mean.
*Patients with a low (<5%) likelihood of coronary disease. †Patients included in the prognostic analysis.
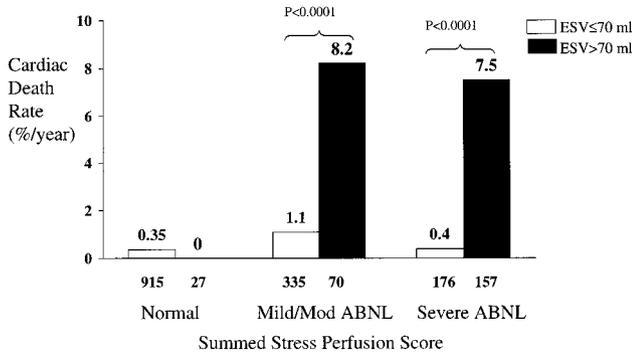
Figure 2. Cardiac death rate (%/year) as a function of perfusion abnormality and ESV. The number of patients within each category is indicated below each column. Abbreviations as in Figure 1.

Figure 3. Cardiac death rate (%/year) as a function of EF and ESV.

EF<45%, stratified by ESV, are shown in Figure 7. Cumulative survival was progressively lower with increasing ESV.

Discussion

This study assessed the prognostic value of gated Tc-99m sestamibi SPECT in patients with known or suspected CAD. Multivariate Cox proportional hazards regression showed that in the prediction of total coronary events, perfusion variables and ESV were independent and powerful predictors, whereas in the prediction of cardiac death, post-stress left ventricular EF and ESV were independent predictors and incremental over perfusion data. ESV demonstrated independent prognostic value for cardiac death after adjustment for EF. Our data show that the criteria of EF<45% and ESV>70 mL, derived

from ROC analysis, efficiently stratify patients into low- and high-risk groups.

Prognostic Value of Post-Stress EF: Incremental Value

Multiple studies have shown that resting and exercise left ventricular EF, measured by radionuclide angiography, are powerful predictors of cardiac events.[6–8,21,22] The Duke investigators showed that exercise radionuclide angiography provides incremental prognostic value over clinical, exercise, and angiographic data in patients with documented CAD.[22]

Few studies have evaluated the incremental prognostic value of perfusion and function, and those that did reported conflicting results.[23,24] These studies used either gated radio-
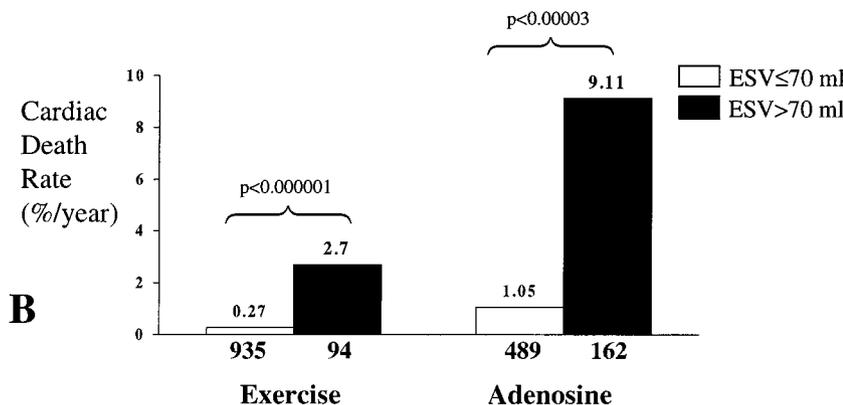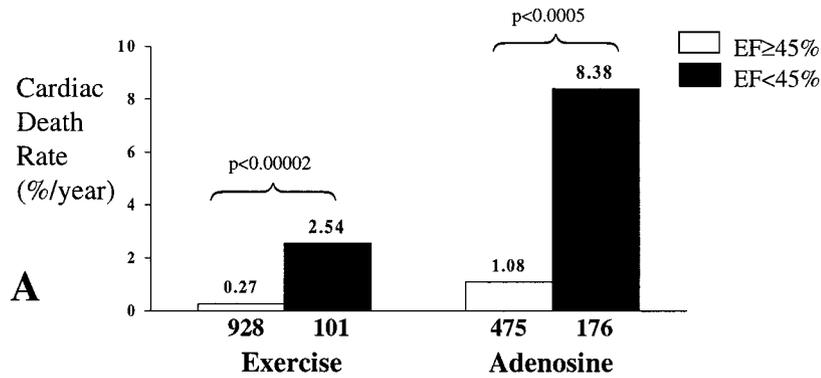

Figure 4. Rates of cardiac death per year in patients undergoing exercise and adenosine stress as a function of (A) EF and (B) ESV.
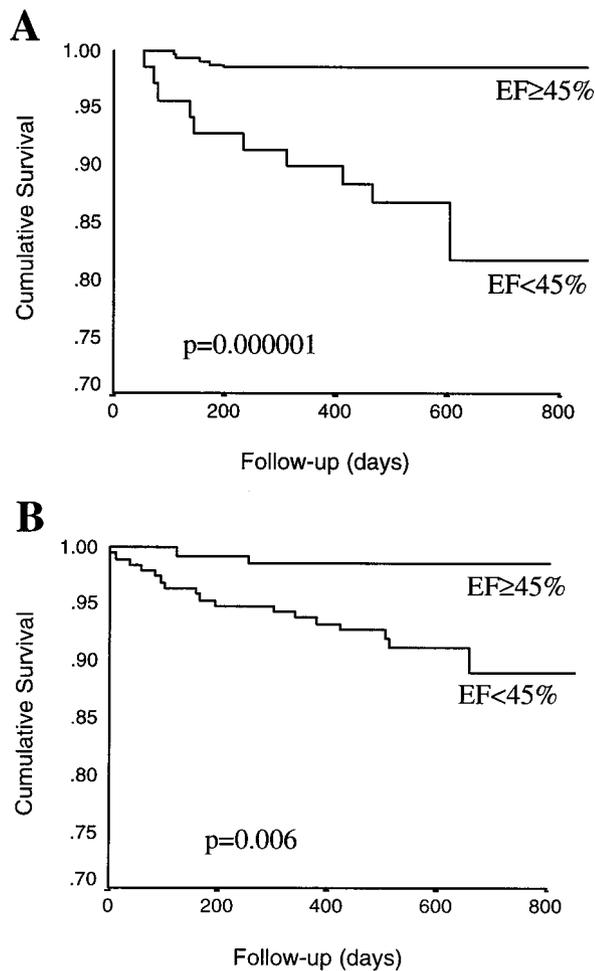
Figure 5. Cumulative survival in (A) patients with mild/moderate perfusion abnormalities and (B) patients with severe perfusion abnormalities, stratified into EF≥45% and EF<45%.
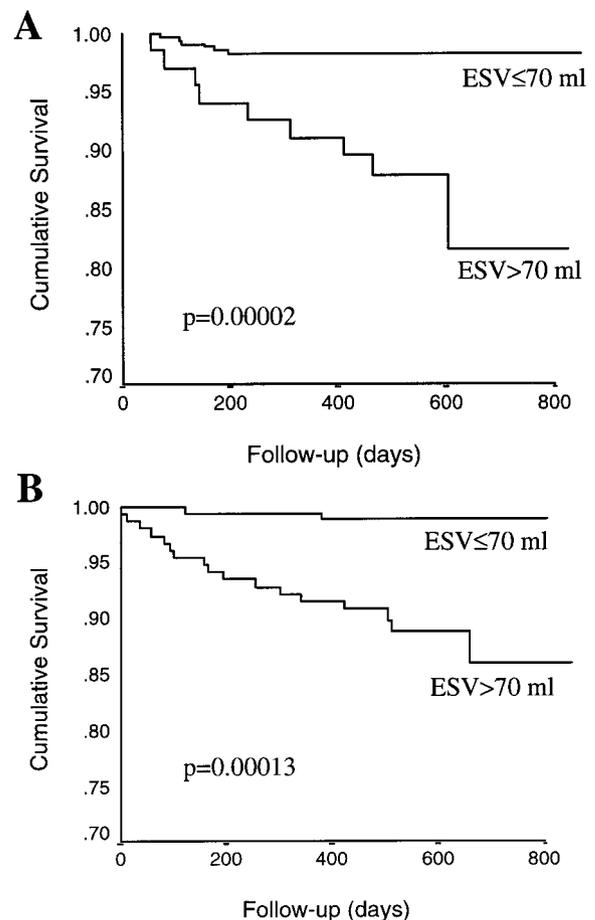

Figure 6. Cumulative survival in (A) patients with mild/moderate perfusion abnormalities and (B) patients with severe perfusion abnormalities, stratified into ESV≤70 mL and ESV>70 mL.

nuclide angiography[23] or first-pass angiography[24] to assess resting EF. Whereas Marie et al[23] showed the incremental prognostic value of perfusion and function, Nallamothu et al[24] found that exercise SPECT perfusion imaging had a much stronger prognostic power than resting EF. Small and selected patient populations likely accounted for these differences.

Our data indicate that post-stress left ventricular EF has significant incremental value over prescan and perfusion variables in predicting cardiac death. As previously shown, cardiac death rate was a function of the extent and severity of perfusion defects at stress.[5] However, further patient stratification by EF showed that patients with an EF≥45% had low cardiac death rates (<1%/year), despite severe perfusion abnormalities.

Prognostic Value of Left Ventricular Volume

No previous study has assessed the incremental value of ESV over perfusion variables in predicting cardiac death. Angiographically measured ESV has been previously reported as a better predictor of survival compared with EF, EDV, and coronary angiographic data in patients after MI[9] and in patients with left ventricular dysfunction who underwent coronary bypass surgery.[10]

In the present study, univariate Cox proportional hazards regression identified both EDV and ESV as highly significant predictors of cardiac death. However, multivariate analysis identified only ESV as an independent predictor of cardiac death after adjustment for prescan, perfusion, and EF data. The threshold of ESV=70 mL, derived by ROC analysis, provided significant stratification of patients into high-risk and low-risk groups. Patients with severe perfusion abnormalities but an ESV≤70 mL had very low cardiac death rates (0.4%/year), whereas patients with only mild/moderate perfusion defects but an ESV>70 mL had high cardiac death rates (8.2%/year).

EF and ESV data provided significant stratification of patients undergoing exercise or adenosine stress. The higher mortality rates in the adenosine group are related to the worse clinical, perfusion, and function characteristics of these patients (Table 2).

Post-Stress Left Ventricular Function and Volume

Ventricular size and function assessed during the first hour after stress incorporates information on baseline and post-stress cardiac function. Johnson et al[12] showed that patients with reversible stress perfusion defects frequently had post-stress (exercise or adenosine) stunning. We recently showed that post-stress stunning is a marker of severe angiographic
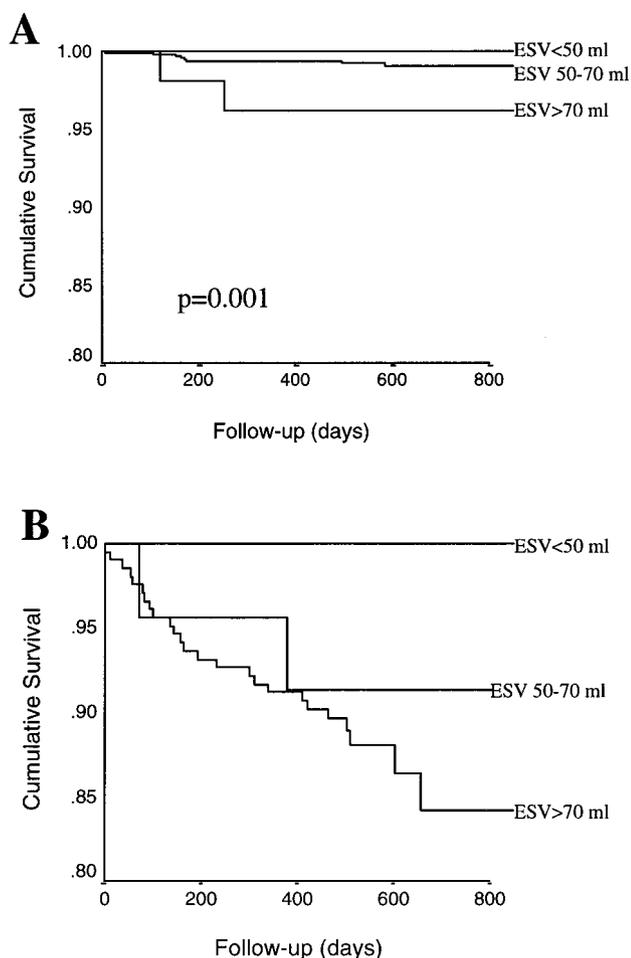
Figure 7. Cumulative survival of patients with (A) EF≥45% and (B) EF<45%, stratified by ESV.

CAD.[25] Our group has also demonstrated the diagnostic value of transient, post-stress dilatation of the left ventricle as a marker of severe and extensive CAD.[26] Therefore, the prognostic value of post-stress ESV and EF may not be solely due to baseline ventricular dilatation and dysfunction; it may also be attributed to transient worsening of ventricular function in patients with stress-induced ischemia.

Referral for Catheterization
Hachamovitch et al[4] showed that referral for cardiac catheterization increased as a function of worsening scan results. Lewin et al[27] preliminarily reported that EF had less impact on referral for catheterization than perfusion information. In the present study, patients referred for early revascularization (≤60 days) had perfusion abnormalities comparable to those of patients experiencing cardiac death, but they had significantly better cardiac function. Patients referred for late (>60 days) revascularization also had similar perfusion abnormalities but better function compared with patients experiencing cardiac death. Multivariate analysis showed that perfusion data were superior to function in predicting total events, 64.7% of which were late revascularization, whereas function data were superior to perfusion in predicting cardiac death. The greater impact of perfusion compared with function information on early referral for revascularization and on the

crossover of patients from medical to revascularization treatment (late revascularization) may account for the higher prognostic power of EF and ESV in the prediction of cardiac death compared with perfusion information, because patients with significant perfusion abnormalities are referred for aggressive treatment. Further incorporation of gated SPECT (EF and ESV) into the decision process of referral for revascularization may result in a reduction of the cardiac death rate.

Study Significance
In contrast to previous studies, which assessed the incremental prognostic value of EF over perfusion[23,24] or ESV over clinical and angiographic information[9,10] in selected patient populations, this study is the first to evaluate the prognostic value of gated SPECT in a large, consecutive patient population who were referred for nuclear testing and the first to incorporate perfusion, EF, and volume. Therefore, our results may be applied to the general population of patients referred for nuclear testing.

Limitations
This study did not evaluate the prognostic value of perfusion and function variables in predicting MI as a separate endpoint because of the small number of MIs during the follow-up period. Further studies with larger patient populations are required to investigate this issue. The frequency of cardiac death was higher than that of nonfatal MI in this population. This unexpected finding my be due to our higher success rate in defining cardiac death.

Conclusions
Post-stress Tc-99m sestamibi gated SPECT provides incremental prognostic information in patients with known or suspected CAD that is better than perfusion data alone. Although perfusion variables are powerful in predicting worsening of coronary disease, post-stress EF and ESV provide incremental value in the prediction of cardiac death. Therefore, the information provided by gated SPECT should be considered in the referral of patients for coronary angiography and revascularization.

References
1. Pollock SG, Abbott RD, Boucher CA, Beller GA, Kaul S. Independent and incremental prognostic value of tests performed in hierarchical order to evaluate patients with suspected coronary artery disease. *Circulation*. 1992;85:237–248.
2. Iskandrian AS, Chae SC, Heo J, Stanberry CD, Wasserleben V, Cave V. Independent and incremental prognostic value of exercise single-photon emission computed tomographic thallium imaging in coronary artery disease. *J Am Coll Cardiol*. 1993;22:665–670.
3. Berman DS, Hachamovitch R, Kiat H, Cohen I, Cabico A, Wang FP, Friedman JD, Diamond GA. Incremental prognostic value and cost implications of normal exercise Tc-99m sestamibi myocardial perfusion SPECT. *J Am Coll Cardiol*. 1995;26:639–547.
4. Hachamovitch R, Berman DS, Kiat H, Cohen I, Cabico JA, Friedman J, Diamond GA. Exercise myocardial perfusion SPECT in patients without

known coronary artery disease: incremental prognostic value and impact on subsequent patient management. *Circulation*. 1996;93:905–914.

5. Hachamovitch R, Berman DS, Shaw LJ, Kiat H, Cohen I, Cabico A, Friedman J, Diamond GA. Incremental prognostic value of myocardial perfusion single photon emission computed tomography for the prediction of cardiac death. *Ciculation*. 1998;97:535–543.

6. Lee KL, Pryor DB, Pieper KS, Harrell FE Jr, Callif RM, Mark DB, Hlatky MA, Coleman RE, Cobb FR, Jones RH. The prognostic value of radionuclide angiography in medically-treated patients with coronary artery disease. *Circulation*. 1990;82:1705–1717.

7. Jones RH, Johnson SH, Bigelow C, Pieper KS, Coleman RE, Cobb FR, Pryor DB, Lee KL. Exercise radionuclide angiocardiography predicts cardiac death in patients with coronary artery disease. *Circulation*. 1991; 84:I52–I58.

8. Pryor DB, Harrel FE Jr, Lee KL, Rosati RA, Coleman RE, Cobb FR, Callif RM, Jones RH. Prognostic indicators from radionuclide angiography in medically treated patients with coronary artery disease. *Am J Cardiol*. 1984;53:18–22.

9. White HD, Norris RM, Brown MA, Brandt PW, Whitlock RM, Wild CJ. Left ventricular end-systolic volume as the major determinant of survival after recovery from myocardial infarction. *Circulation*. 1987;76:44–51.

10. Hamer AW, Takayama M, Abraham KA, Roche AH, Kerr AR, Williams BF, Ramage MC, White HD. End-systolic volume and long-term survival after coronary artery bypass surgery in patients with impaired left ventricular function. *Circulation*. 1994;90:2899–2904.

11. Germano G, Kiat H, Kavanagh PB, Moriel M, Mazzanti M, Su HT, Van Train KF, Berman DS. Automatic quantification of ejection fraction from gated myocardial perfusion SPECT. *J Nucl Med*. 1995;36:2138–2147.

12. Johnson LL, Verdesca SA, Aude WY, Xavier RC, Nott LT, Campanella MW, Germano G. Postischemic stunning can affect left ventricular ejection fraction and regional wall motion on post-stress gated sestamibi tomograms. *J Am Coll Cardiol*. 1997;30:1641–1648.

13. Iskandrian AE, Germano G, VanDecker W, Ogilby JD, Wolf N, Mintz R, Berman DS. Validation of left ventricular volume measurements by gated SPECT Tc-99m sestamibi imaging. *J Nucl Cardiol*. 1998;5:574–578.

14. Chua T, Kiat H, Germano G, Maurer G, Van Train K, Friedman J, Berman D. Gated technetium-99m sestamibi for simultaneous assessment of stress myocardial perfusion, post-exercise regional ventricular function and myocardial viability: correlation with echocardiography and rest thallium-201 scintigraphy. *J Am Coll Cardiol*. 1994;23:1107–1114.

15. Staniloff HM, Forester JS, Berman DS, Swan HJC. Prediction of death, myocardial infarction, and worsening chest pain using thallium scintigraphy and exercise electrocardiography. *J Nucl Med*. 1986;27:1842–1848.

16. Ladenheim ML, Pollock BH, Rozanski A, Berman DS, Staniloff HM, Forrester JS, Diamond GA. Extent and severity of myocardial hypoperfusion as predictors of prognosis in patients with suspected coronary artery disease. *J Am Coll Cardiol*. 1986;7:464–471.

17. Diamond GA, Staniloff HM, Foreester JS, Pollock BH, Swan HJC. Computer assisted diagnosis in the noninvasive evaluation of patients with suspected coronary artery disease. *J Am Coll Cardiol*. 1983;1: 444–455.

18. Berman DS, Kiat H, Friedman JD, Wang FP, Van Train K, Matzer L, Maddahi J, Germano G. 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;22:1455–1464.

19. Penell DJ, Mavrogeni IS, Forbat SM, Karwatowski SP, Underwood SR. Adenosine combined with dynamic exercise for myocardial perfusion imaging. *J Am Coll Cardiol*. 1995;25:1300–1309.

20. Germano G, Kavanagh PB, Chen J, Waechter P, Su HT, Kiat H, Berman DS. Operator-less processing of myocardial perfusion SPECT studies. *J Nucl Med*. 1995;36:2127–2132.

21. The Multicenter Postinfarction Research Group. Risk stratification and survival after myocardial infarction. *N Engl J Med*. 1983;310:331–336.

22. Shaw LJ, Heinle SK, Borges-Net S, Kesler K, Coleman RE, Johns RH. Prognosis by measurements of left ventricular function during exercise. *J Nucl Med*. 1998;39:140–146.

23. Marie PY, Danchin N, Durand JF, Feldmann L, Grentzinger A, Olivier P, Karcher G, Juillière Y, Virion J, Beurrier D, Cherrier F, Bertrand A. Long-term prediction of major ischemic events by exercise thallium-201 single-photon emission computed tomography: incremental prognostic value compared with clinical exercise testing, catheterization, and radionuclide angiographic data. *J Am Coll Cardiol*. 1995;26:879–886.

24. Nallamothu N, Araujo L, Russel J, Heo J, Iskandrian AE. Prognostic value of simultaneous perfusion and function assessment using Technetium-99m sestamibi. *Am J Cardiol*. 1996;78:562–563.

25. Sharir T, Bacher-Stier C, Dhar S, Lewin HC, Friedman J, Germano G, Berman DS. Post-exercise regional wall motion abnormalities detected by Tc-99m sestamibi gated SPECT: a marker of severe coronary artery disease. *J Nucl Med*. 1998;39:87P. Abstract.

26. Mazzanti M, Germano G, Kiat H, Kavanagh PB, Alexanderson E, Friedman JD, Hachamovitch R, Van Train KF, Berman DS. Identification of severe and extensive coronary artery disease by automatic measurement of transient ischemic dilation of the left ventricle in dual-isotope myocardial perfusion SPECT. *J Am Coll Cardiol*. 1996;27:1612–1620.

27. Lewin HC, Germano G, Friedman JD, Cohen I, Kang X, Berman DS. The impact of gated SPECT on the rate of early referral to catheterization following myocardial perfusion SPECT. *J Nucl Med*. 1998;39:87P. Abstract.

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