Usefulness of Stress Gated Technetium-99m Single Photon Emission Computed Tomographic Myocardial Perfusion Imaging for the Prediction of Cardiac Death in Patients With Moderate to Severe Left Ventricular Systolic Dysfunction and Suspected Coronary Artery Disease

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Although stress gated technetium-99m single-photon emission computed tomographic (SPECT) myocardial perfusion imaging (MPI) is useful in differentiating ischemic from nonischemic cardiomyopathy, its prognostic usefulness in this patient population is not well understood. Consecutive unique patients with suspected coronary artery disease who, for clinical indications, underwent technetium-99m rest and stress MPI demonstrating ejection fractions ≤40% by gated SPECT imaging were retrospectively identified. In addition to prescan variables, previously defined cutoffs for gated SPECT parameters using visual and standard 17-segment semiquantitative scoring were applied and related to the occurrence of cardiac death up to 5 years after MPI. Of the 475 patients fulfilling criteria for study inclusion, follow-up was complete in 444 (93%) over 3.7 ± 1.6 years. Of 393 patients without subsequent early (≤60 days) coronary revascularization, cardiac death occurred in 64 (16%). The summed stress score, an MPI measure of the extent and severity of coronary artery disease that also accounts for the ischemic burden, was the gated SPECT parameter most related to cardiac death with Kaplan-Meier 5-year cardiac death–free survival of 85.6% and 67.3% in patients with summed stress scores ≤8 and >8, respectively (p <0.001). In multivariate Cox regression analysis, a summed stress score >8 independently contributed to cardiac death (adjusted hazard ratio 2.20, 95% confidence interval 1.34 to 3.61), and its addition to the model significantly increased the global chi-square value over prescan variables (from 32.46 to 41.67, p = 0.002). In conclusion, stress MPI data from gated technetium-99m SPECT scans are useful for the prediction of cardiac death in patients with moderate to severe left ventricular systolic dysfunction in whom there is suspicion of underlying coronary artery disease. **(Am J Cardiol 2012;109:26–30)**

Differentiating ischemic from nonischemic cardiomyopathy is of considerable importance for optimal patient management. Our group[1,2] and others[3,4] have previously demonstrated that stress gated technetium-99m single-photon emission computed tomographic (SPECT) myocardial perfusion imaging (MPI) is useful in differentiating ischemic from nonischemic cardiomyopathy. While the findings from these studies have important diagnostic implications, the prognostic usefulness of this cardiovascular imaging technique in this patient population is not well understood. Accordingly, in the present study, we examined the usefulness of stress gated technetium-99m SPECT MPI for the prediction of cardiac death in patients with moderate to severe left ventricular systolic dysfunction and suspected coronary artery disease (CAD).

Methods

The electronic database within the Nuclear Cardiology Laboratory at Hartford Hospital (Hartford, Connecticut) was queried to identify consecutive unique patients who, for clinical indications, underwent technetium-99m sestamibi rest and stress MPI from January 1, 1996, to December 31, 2004, inclusive, with ejection fractions ≤40% by gated SPECT imaging. Excluded were patients with any of the following at the time of MPI: (1) known significant CAD (≥50% stenosis in any major epicardial vessel by angiography), (2) previous coronary revascularization, or (3) previous myocardial infarction as documented by clinical history or as defined by associated changes (Q-waves or QS complexes in the absence of QRS prolongation[5]) on rest electrocardiography. Also excluded were patients with implanted cardiac de-

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fibrillators or pacemakers at the time of MPI. Patients fulfilling criteria for study inclusion but having undergone coronary revascularization procedures early (≤60 days) after MPI were excluded from the prognostic portion of the analysis.[6] This study was approved by and conducted within guidelines of the institutional review board at Hartford Hospital.

Exercise and pharmacologic stress testing was performed in accordance with standard protocols and techniques.[7] Radiopharmaceutical dosing, gated SPECT acquisition, and image processing were performed using methods previously described[2] and within guidelines established by the American Society of Nuclear Cardiology.[8] Notably, our laboratory currently uses the same gated SPECT protocol for rest and stress technetium-99m MPI except now with attenuation correction.[9]

All images were visually interpreted during daily reading sessions by a consensus of ≥2 experienced readers without clinical information using a standard 17-segment model and semiquantitative scoring.[10] For the assessment of myocardial perfusion on stress and rest imaging, each segment was scored on a scale of 0 to 4 (0 = normal activity, 1 = mild, 2 = moderate, 3 = severe reduction in photon activity, 4 = complete absence of photon activity). For each image, a summed stress score and a summed rest score was calculated by adding the segment scores. A summed difference score was derived for each image by subtracting the summed rest score from the summed stress score. Evaluation of left ventricular systolic function on the stress images was performed by assessment of endocardial border excursion and regional wall thickening with each segment scored on a scale of 0 to 5 (0 = normal, 1 = mild, 2 = moderate, 3 = severe hypokinesia, 4 = akinesia, 5 = dyskinesia). The variance of the average wall motion score for left anterior descending, circumflex and right coronary artery vascular territories was expressed as the regional wall motion variance. The ejection fraction was calculated using an automated quantitative method[11] and confirmed visually. On the basis of previously reported data from our group,[1] identified upper bounds of the 95% confidence intervals for nonischemic cardiomyopathy (8.39, 1.94, and 0.114 for the summed stress score, summed difference score, and regional wall motion variance, respectively) were applied as previously described.[2]

Patient follow-up was achieved through mailed questionnaires and/or scripted telephone interviews as well as by review of hospital admission records and the Social Security Death Index. In patients who were confirmed to have died, experienced personnel unaware of MPI data reviewed information provided by hospital admission records or death certificates to ascertain cause, which was categorized as cardiac (death attributable to lethal arrhythmia, heart failure, myocardial infarction, or sudden death) or noncardiac. Follow-up was considered incomplete if a surviving patient was with <1 year of data (by questionnaire, telephone interview, or hospital admission records) or apparent death in a patient could not be confirmed to ascertain cause. Patients were followed for up to 5 years after MPI.

All numerical values are presented as mean ± SD or as proportions. Discrete or dichotomized variables were compared using chi-square or Fisher's exact tests and continuous variables using Student's *t* tests. Cumulative cardiac death–free survival was calculated using the Kaplan-Meier procedure and compared using the log-rank test. Annualized rates of cardiac death were calculated as the number of occurrences divided by the total exposure years. Multivariate Cox regression was used to identify variables that independently contributed to cardiac death. A forward stepwise (Wald method) selection procedure was applied with prescan followed by gated SPECT imaging and thresholds of $p \leq 0.05$ and $p \geq 0.10$ for variable entry and removal, respectively. A p value <0.05 was considered statistically significant. All statistical analyses were 2 tailed and performed using SPSS version 15.0 (SPSS, Inc., Chicago, Illinois).

Table 1
Characteristics of the study patients (n = 444)

Variable	Value
Age (years)	63 ± 13 (25–88)
Men	285 (64%)
History	
Chest pain or dyspnea	332 (75%)
Heart failure	189 (43%)
Angina pectoris	153 (34%)
Systemic hypertension	344 (77%)
Tobacco smoker	239 (54%)
Diabetes mellitus	162 (36%)
Hypercholesterolemia	137 (31%)
Cardiac medications	
Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers	231 (52%)
Diuretics	208 (47%)
β blockers	186 (42%)
Aspirin	166 (37%)
Statins	93 (21%)
Digoxin	76 (17%)
Calcium antagonists	72 (16%)
Nitrate	68 (15%)

Data are expressed as mean ± SD (range) or as number (percentage).

Results

Of the 475 patients fulfilling criteria for study inclusion, follow-up was complete in 444 (93%) over 3.7 ± 1.6 years. The prescan characteristics of these 444 patients are listed in Table 1. Notably, 70% of patients possessed multiple CAD risk factors. Seventy-six percent of patients underwent pharmacologic stress. On gated SPECT imaging, the mean ejection fraction in the patients was 30.8 ± 7.3%. Fifty-five percent of patients demonstrated ≥1 of the following: summed stress score >8 (37%), regional wall motion variance >0.114 (36%), or summed difference score >1 (28%). Substantial reversibility (summed difference score >8) was demonstrated in 5% of patients.

Fifty-one patients (11%) subsequently underwent early coronary revascularization (coronary artery bypass grafting in 32 and percutaneous coronary intervention in 19). Gated SPECT parameters in relation to early coronary revascularization are listed in Table 2. Of 393 patients without early coronary revascularization, cardiac death occurred in 64 (16%). Cumulative 5-year cardiac death–free survival in these 393 patients was 79.9%, while the rate of cardiac death was 4.3% per year.

Prescan and gated SPECT variables in relation to cardiac death are listed in Table 3. Because the summed stress score was the gated SPECT parameter most related to cardiac death, its prognostic usefulness was examined. The ejection fraction

Table 2
Gated technetium-99m single-photon emission computed tomographic parameters in relation to early coronary revascularization

Variable	No Early Revascularization (n = 393)	Early Revascularization (n = 51)	p Value
Summed stress score	6.9 ± 6.1	13.2 ± 7.0	<0.001
Summed stress score >8	127 (32%)	38 (75%)	<0.001
Summed difference score	1.3 ± 2.6	5.1 ± 5.0	<0.001
Summed difference score >1	90 (23%)	36 (71%)	<0.001
Regional wall motion variance	0.237 ± 0.579	0.512 ± 0.696	0.009
Regional wall motion variance >0.114	131 (33%)	29 (57%)	0.001
Summed stress score >8 or summed difference score >1 or regional wall motion variance >0.114	197 (50%)	46 (90%)	<0.001
Ejection fraction (%)	30.6 ± 7.5	32.4 ± 6.1	0.062

Data are expressed as mean ± SD or as number (percentage).

Table 3
Prescan and gated technetium-99m single-photon emission computed tomographic variables in relation to cardiac death

Variable	No Cardiac Death (n = 329)	Cardiac Death (n = 64)	p Value
Age (years)	62 ± 13	66 ± 13	0.030
Age ≥70 years	104 (32%)	31 (48%)	0.009
Men	214 (65%)	39 (61%)	0.530
Chest pain or dyspnea	243 (74%)	43 (67%)	0.273
Heart failure	150 (46%)	28 (44%)	0.786
Angina pectoris	99 (30%)	22 (34%)	0.497
Systemic hypertension	258 (78%)	42 (66%)	0.028
Tobacco smoker	180 (55%)	29 (45%)	0.168
Diabetes mellitus	120 (37%)	22 (34%)	0.749
Hypercholesterolemia	104 (32%)	10 (16%)	0.010
Pharmacologic stress	237 (72%)	59 (92%)	0.001
Summed stress score	6.4 ± 5.7	9.2 ± 7.3	0.006
Summed stress score >8	94 (29%)	33 (52%)	<0.001
Summed difference score	1.2 ± 2.6	1.7 ± 3.0	0.232
Summed difference score >1	73 (22%)	17 (27%)	0.446
Regional wall motion variance	0.212 ± 0.505	0.366 ± 0.859	0.171
Regional wall motion variance >0.114	108 (33%)	23 (36%)	0.629
Ejection fraction (%)	30.8 ± 7.3	29.6 ± 8.4	0.232

Data are expressed as mean ± SD or as number (percentage).

on gated SPECT imaging was not significantly different between patients with summed stress scores ≤8 and those with scores >8 (30.8 ± 7.4% vs 30.4 ± 7.6%, respectively, p = 0.643). Cumulative 5-year cardiac death–free survival was 85.6% and 67.3% in patients with summed stress scores ≤8 and >8, respectively (p <0.001; Figure 1). The annualized cardiac death rate in patients with summed stress scores ≤8 (2.9%) was significantly lower than in those with summed stress scores >8 (7.3%, unadjusted hazard ratio 2.62, 95% confidence interval 1.58 to 4.33, p <0.001).

Of the variables listed in Table 3 and as listed in Table 4, there were 5 that independently had significant effects on cardiac death. The addition of the summed stress score to the model significantly increased the global chi-square value over prescan variables (from 32.46 to 41.67, p = 0.002). Risk-adjusted cardiac death–free survival in relation to the summed stress score is shown in Figure 2.

Discussion

In patients with moderate to severe left ventricular systolic dysfunction for whom there was clinical suspicion for underlying CAD, we have demonstrated that gated technetium-99m SPECT imaging has prognostic usefulness. In the prediction of cardiac death, stress MPI was found to be the most important gated SPECT parameter and by use of visual and standard semiquantitative scoring provided a significant estimation of risk.

Bart et al[12] found that the extent of angiographically diagnosed CAD contributed more independent prognostic information than the clinical diagnosis of ischemic or nonischemic cardiomyopathy. Moreover, patients with the clinical diagnosis of ischemic cardiomyopathy, but only mild disease on angiography, had a mortality rate similar to those with nonischemic cardiomyopathy. To further elucidate the association between the extent of CAD and mortality aimed at more accurate prognostication, Felker et al[13] assessed the clinical history and coronary anatomy in patients with symptomatic heart failure and found that the "modified number-of-diseased-vessels classification (0/1, 2, 3)" scheme provided the most independent prognostic power. In the present analysis, the summed stress score, an MPI measure of the extent and severity of CAD that also accounts for the ischemic burden, independently contrib-

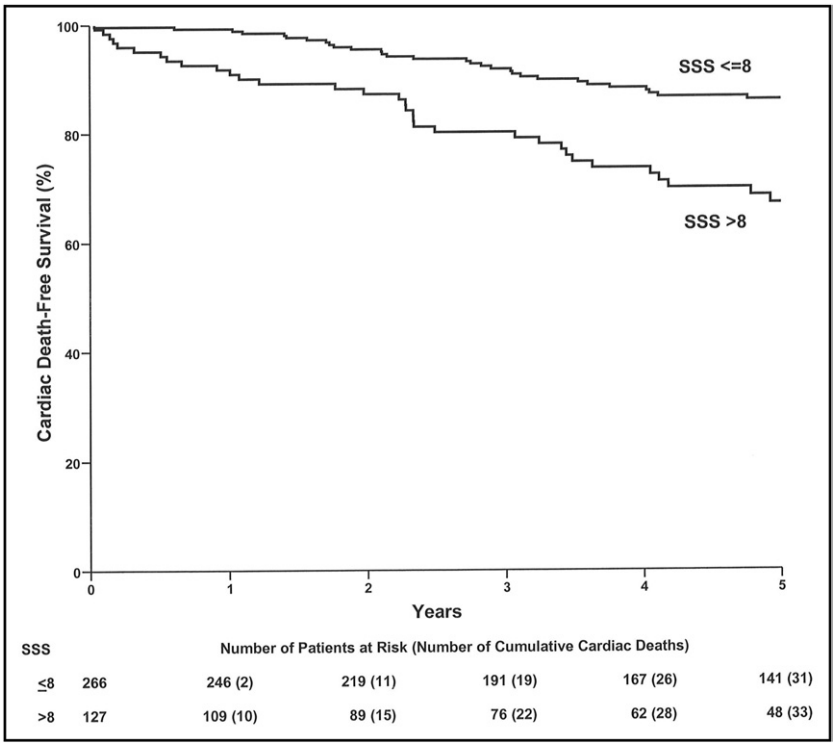

Figure 1. Kaplan-Meier 5-year cardiac death–free survival plots in patients with summed stress scores (SSS) ≤8 versus >8.

Table 4
Variables independently affecting cardiac death

Variable	Hazard Ratio	95% Confidence Interval	p Value
Summed stress score >8	2.20	1.34–3.61	0.002
Pharmacologic stress	3.88	1.53–9.79	0.004
Hypercholesterolemia	0.39	0.20–0.77	0.007
Age ≥70 years	1.85	1.13–3.04	0.014
Systemic hypertension	0.57	0.33–0.95	0.034

uted to cardiac death. After adjusting for important prescan variables, patients with summed stress scores >8 were 2 times more likely than those with summed stress scores ≤8 to die from cardiac causes. This finding substantiates and extends that from our earlier work,[2] wherein the same parameter and defined cutoff correctly identified most patients with ischemic cardiomyopathy and was the single most important variable to differentiate ischemic from nonischemic cardiomyopathy according to the angiographic definition proposed by Felker et al.[13] Hence, using gated technetium-99m SPECT imaging in the diagnostic assessment of patients with cardiomyopathy, early referral of those with stress perfusion abnormalities encompassing a substantial amount of the myocardium for coronary angiography is an important consideration because of the increased probability for an ischemic cause and, as such, the potential survival benefit that is derived from revascularization.[14,15] Conversely, a nonischemic pathophysiologic process is the probable cause in patients with stress perfusion that is either normal or abnormal but involving a minimal amount of the myocardium. Any underlying CAD in such patients is likely of limited prognostic significance, and thus, noninvasive therapeutic regimens would appear most appropriate as an initial management strategy, particularly in those without demonstrable ischemia.

In our earlier work,[2] reversibility in stress MPI abnormalities enhanced gated technetium-99m SPECT identification of ischemic cardiomyopathy. In the present analysis, the summed difference score was not found to be associated with an increased risk for cardiac death. A possible explanation for this finding is that reversibility in stress MPI abnormalities was associated with early coronary revascularization and may have affected cardiac outcomes. Recently reported findings in patients with confirmed ischemic cardiomyopathy indicate that fulfillment of criteria for myocardial viability plus ischemia on gated technetium-99m SPECT imaging independently predicts cardiac death.[16]

In the present analysis, pharmacologic stress independently contributed to cardiac death. In patients with cardiomyopathy, the higher cardiac risk in those referred for pharmacologic stress MPI reflects not only the presence of co-morbidities but also more severe heart failure symptoms, all of which worsen prognosis.[12,13] The finding that cardiac death was less likely to occur in patients with histories of hypercholesterolemia or systemic hypertension was unexpected. In accordance with our earlier work,[2] patients with known significant CAD or previous myocardial infarction at the time of MPI were excluded, which may explain this finding. Another possible explanation is that medical therapies in relation to these CAD risk factors favorably affected cardiac prognosis.

The present analysis had limitations. This was a retrospective study. Referral bias for coronary angiography versus MPI as the initial diagnostic procedure may have affected the CAD and co-morbidity risk profiles of our patient population.[17] Concurrent antianginal drug therapy at the time of MPI may have

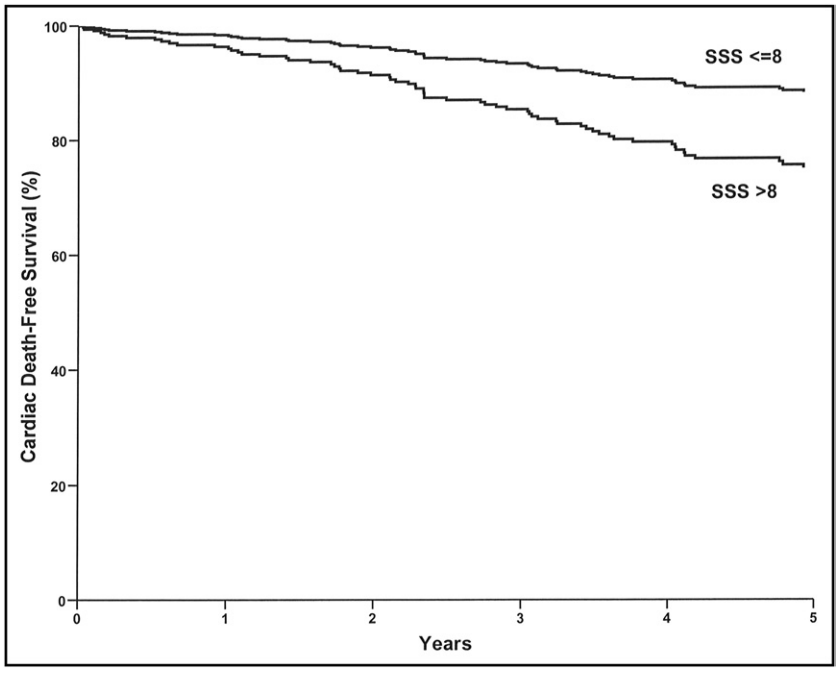

Figure 2. Cox proportional (risk-adjusted) 5-year cardiac death–free survival plots in relation to the summed stress score (SSS) ≤8 versus >8.

resulted in underestimation of the presence and severity of ischemia.[18] Referral bias for coronary revascularization versus medical therapy as the initial management strategy may have affected our prognostic findings.

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