The prognostic value of ECG-gated SPECT imaging in patients undergoing stress Tc-99m sestamibi myocardial perfusion imaging

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Background. **The ability of stress radionuclide myocardial perfusion imaging to predict adverse cardiac events is well accepted. As left ventricular systolic function has also been shown to be an important prognostic indicator, the objective of this study was to determine whether electrocardiography (ECG)–gated single photon emission computed tomography (SPECT) functional data add additional power.**

Methods and Results. **In this study 3207 patients who underwent stress myocardial perfusion imaging with ECG gating, without early (≤60 days) revascularization, were studied. Subsequent nonfatal myocardial infarction and cardiac death were related to perfusion and ECG-gated SPECT ventricular function parameters. Cox proportional hazards regression analysis was used to evaluate the independent predictive value of these parameters, as well as their added utility over clinical and ECG parameters. Patients with abnormal perfusion images had an annual event rate of 5.1% compared with 1.6% for patients with normal images ($P < .001$). An abnormal gated SPECT wall motion score was associated with an annual event rate of 6.1% compared with 1.6% for a normal score ($P < .001$), and an abnormal left ventricular ejection fraction was associated with an event rate of 7.4% compared with 1.8% for normal patients ($P < .001$). Abnormal ECG-gated SPECT results worsened outcome in both patients with normal perfusion images and those with abnormal perfusion images. Cardiac death was predicted by the number of territories with a perfusion defect and an abnormal ejection fraction, whereas myocardial infarction was predicted by the number of territories with a perfusion defect but not by ejection fraction.**

Conclusions. **Ventricular function data from ECG-gated SPECT add important prognostic value to data obtained from perfusion imaging alone in predicting adverse cardiac events. (J Nucl Cardiol 2004;11:253-62.)**

Key Words: Single photon emission computed tomography myocardial perfusion imaging • electrocardiographic gating

Left ventricular systolic function is one of the strongest predictors of cardiac death in patients with cardiovascular disease.[1] Patients with normal or near-normal ventricular function have an excellent prognosis, even in the presence of coronary artery disease, whereas patients with poor ventricular function are at high risk for death, particularly if ischemia is present.[2,3]

Findings on stress radionuclide myocardial perfusion single photon emission computed tomography (SPECT) imaging are also important predictors of adverse cardiac events. The extent and severity of perfusion abnormalities have been shown to be superior to clinical and electrocardiographic data in risk-stratifying patients.[4,5]

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The advent of technetium 99m–based perfusion tracers, such as Tc-99m sestamibi, initiated the simultaneous assessment of myocardial perfusion and ventricular systolic function through the use of gating techniques. Although several groups have reported that the addition of functional information from electrocardiography (ECG)–gated SPECT enhances the diagnostic accuracy of stress perfusion imaging,[6-9] the prognostic value of ECG-gated perfusion imaging is less appreciated.[10,11]

Therefore the objective of this study was to evaluate risk stratification in a large series of patients who underwent rest/stress ECG-gated Tc-99m sestamibi SPECT myocardial perfusion imaging in two large clinical centers. The prognostic value of ventricular function information from ECG-gated SPECT was explored in detail, particularly in relation to perfusion image results.

METHODS

Patients

From a nuclear cardiology database compiled at two teaching hospitals over a period of approximately 2 years (September 1995 to December 1997), consecutive patients who underwent stress Tc-99m sestamibi SPECT myocardial perfusion imaging with gated imaging were identified. From a total of 4256 patients tested during that interval, 3724 had complete gated SPECT data (age ≥20 years). Follow-up was available in 91.1% (3392 patients). Patients who had a revascularization procedure within 60 days after stress testing (n = 185) were excluded.[12] The study group therefore consisted of 3207 patients.

Stress Testing and Imaging

Patients underwent treadmill exercise (59% of patients), dipyridamole (36%), adenosine (<1%), or dobutamine (5%) stress testing by use of standard techniques.[13-16] Radiotracer dosing, image protocols, and processing are as previously described.[17] One-day rest/stress protocols were used for 76% of patients, two-day protocols for 17%, and dual-isotope protocols for less than 1%. Some patients with normal images (6%) did not undergo rest imaging. No attenuation correction was used in this study. ECG gating was performed on the poststress images at 8 frames per cardiac cycle, with a 40% acceptance window (expanded up to 100% at the discretion of the technologist).

Image Interpretation and Scoring

The images were interpreted during daily clinical reading sessions by consensus of 2 or more experienced observers. Interpretation and scoring were performed before review of clinical data.

For the SPECT perfusion images, 8 left ventricular regions—anterior, anteroseptal, inferoseptal, inferior, inferolateral, anterolateral, anteroapex, and inferoapex—were qualitatively classified as having no defect, a fixed defect, a totally reversible defect, or a partially reversible defect. For severity, each region on the stress images was scored from 0 to 4 (normal to no counts). For each stress image, the severity scores were added to derive a summed stress score (SSS) (range, 0-32). Individual vascular territories that were considered to contain defects resulting only from artifacts were classified as normal. An SSS of 0 or 1 was considered to indicate normal perfusion, an SSS of 2 or 3 indicated mildly abnormal perfusion, an SSS of 4 or 5 indicated moderately abnormal perfusion, and an SSS of 6 or greater indicated severely abnormal perfusion. (It should be noted that the perfusion images were scored before publication of standard American Society of Nuclear Cardiology scoring methods.[18,19] The SSS scores described in this article and our method of categorizing the patients can be extrapolated to a 20-segment analysis by multiplying our scores by 2.5.[20])

Perfusion in the left anterior descending, left circumflex, and right coronary artery territories was qualitatively classified as normal, fixed defect, partially reversible defect, or totally reversible defect. By this classification, the number of vascular territories with a perfusion defect was determined. For the most part, defects in the anterior, anteroseptal, and anteroapical walls were considered to be in the territory of the left anterior descending artery; defects in the inferior, inferoseptal, and inferoapical walls were considered to be in the territory of the right coronary artery; and defects in the anterolateral and inferolateral walls were considered to be in the territory of the left circumflex artery. However, the image interpreters could use their judgement based on the defect patterns. Images were also subjectively assessed for the presence of fixed or reversible left ventricular cavity dilatation.[21]

In the assessment of ventricular function, 5 regions were considered—anterior, lateral, inferior, septum, and apex—and were classified as having normal motion/thickening (score = 0), being mildly hypokinetic (score = 1), being moderately hypokinetic (score = 2), being severely hypokinetic (score = 3), being akinetic (score = 4), or being dyskinetic (score = 5).[18] For each patient, the gated SPECT scores were added to obtain a wall motion score (range, 0-25). The left ventricular ejection fraction (LVEF) was also derived based on the QGS (quantitative gated SPECT) program developed by Germano et al.[22] The calculated LVEF was confirmed visually. Gated SPECT images were considered normal when LVEF was 50% or greater[11] or wall motion score was 1 or lower. Both the wall motion scores and the ejection fractions were used in the analyses, as it is possible for a patient to have an abnormal gated SPECT image with a regional wall motion abnormality yet have a preserved or normal ejection fraction (ie, because of compensation by normally functioning myocardial regions).

Follow-up

Patient follow-up was obtained by a combination of scripted telephone interviews and letters. A review of hospital admission/database records, the public Social Security database, and death certificates was performed to confirm events. Cardiac events considered were nonfatal myocardial infarction (MI) and cardiac death. If a patient was found to have more than one event after nuclear testing, the more serious event (cardiac death) was counted.[23]

Table 1. Clinical characteristics

	All patients (n = 3207)	Event-free (n = 3027)	Cardiac event (n = 180)
Age (y)	61.9 ± 12.8	61.4 ± 12.7	69.6 ± 12.2‡
Gender (M/F)	1620/1587	1521/1506	99/81
Reason for study			
Chest pain (%)	1396 (44)	1354 (45)	42 (23)‡
Recent MI (%)	169 (5)	154 (5)	15 (8)
Preoperatively (%)	152 (5)	132 (4)	20 (11)‡
Assess known CAD (%)	937 (29)	876 (29)	61 (34)
Other (%)	553 (17)	511 (17)	42 (23)
Pretest likelihood of CAD*	63.7 ± 37.6	63.1 ± 37.6	72.4 ± 37.0‡
Past history			
MI (%)	777 (24)	714 (24)	63 (35)‡
CABG and/or PCI (%)	789 (25)	731 (24)	58 (32)†
Cardiac risk factors			
Diabetes mellitus (%)	756 (24)	674 (22)	82 (46)‡
Hypertension (%)	1756 (55)	1628 (54)	128 (71)‡
Hyperlipidemia (%)	1327 (41)	1252 (41)	75 (42)
Smoking (%)	988 (31)	939 (31)	49 (27)

Numbers in parentheses refer to the percentage of patients in the column who have the particular variable. *P* values compare these percentages between the event-free and cardiac event columns.
CAD, Coronary artery disease; *CABG,* coronary artery bypass grafting; *PCI,* percutaneous coronary intervention.
*Thirty-five patients have missing values.
†$P < .05$ compared with event-free. For the pretest likelihood variable, this applies to the distribution of categories excluding the known CAD category.
‡$P < .001$ compared with event-free.

Statistical Analysis

In preliminary analyses we compared distributions and means of variables between subjects with and without events. Continuous variables were described as mean ± 1 SD and compared by use of *t* tests. Categorical variables were described as percentages and compared by use of the χ^2 or Fisher exact test. Time-to-event analyses were performed by Kaplan-Meier analyses. If a patient was found to have more than one event during follow-up, the more serious event (cardiac death) was counted. Patients who underwent early (≤60 days) revascularization were excluded. Annual event rates were calculated as the number of events divided by the sum of each individual follow-up period in years.

Cox proportional hazards regression analysis was performed to identify independent predictors of events. The variables listed in Tables 1 and 2 were considered for this analysis, but only those that achieved statistical significance by univariate analysis were entered into the Cox analysis. $P < .05$ was considered significant.

RESULTS

Clinical Characteristics

Over a mean follow-up of 2.24 ± 1.32 years (up to 6.6 years), 180 patients (5.6%) had a cardiac event. Of these, 61 (2.2%) had a nonfatal MI and 119 (3.7%) cardiac death (10 of these deaths followed infarction). As shown in Table 1, patients who had a cardiac event were significantly older, were more often referred for stress testing for reasons other than chest discomfort, had a higher pretest likelihood of coronary disease, more often had a prior history of cardiac disease including MI and previous revascularization, and more often had diabetes and hypertension. Table 2 shows that patients who had a cardiac event more often underwent pharmacologic stress, more often had an abnormal baseline ECG, and had a more frequent uninterpretable ECG response to stress. The occurrence of stress-induced ECG ischemia was similar in patients with and without an event.

Relationship of Perfusion Imaging Results to Cardiac Events

All perfusion and functional results were significantly more abnormal in patients who had a cardiac event compared with event-free patients (Table 2). Over the entire follow-up period, patients with abnormal perfusion images (SSS ≥2) had a cumulative event rate of 9.5% (117/1237) whereas those with normal perfusion images had an event rate of 3.2% (63/1970) ($P < .001$).

Table 2. ECG and imaging Results

	All patients (n = 3207)	Event-free (n = 3207)	Cardiac event (n = 180)
Pharmacologic stress (%)	1344 (42)	1206 (40)	138 (77)‡
Baseline ECG abnormal (%)	1445 (46)	1429 (47)	116 (65)‡
Stress ECG response*			
Ischemia (%)	953 (30)	900 (30)	53 (29)
No ischemia (%)	1970 (61)	1876 (62)	94 (52)
Uninterpretable (%)	175 (6)	151 (5)	24 (13)‡
ST elevation (%)	19 (1)	17 (1)	2 (1)
Perfusion Images			
Normal (SSS ≤1) (%)	1970 (61)	1907 (63)	63 (35)‡
Abnormal (SSS ≥2) (%)	1237 (39)	1120 (37)	117 (65)‡
Ischemia (%)	892 (28)	816 (27)	76 (42)‡
No. of vascular territories with perfusion defect	0.54 ± 0.71	0.52 ± 0.69	1.03 ± 0.87‡
MVD pattern (%)	338 (11)	286 (9)	52 (29)‡
MVD ischemia (%)	151 (5)	130 (4)	21 (12)‡
SSS	2.14 ± 3.25	2.03 ± 3.19	3.95 ± 3.71‡
Reversible LV dilatation (%)	104 (3)	87 (3)	17 (9)‡
Gated SPECT			
Wall motion score	1.79 ± 3.55	1.63 ± 3.37	4.46 ± 5.05‡
Wall motion score ≥2 (%)	909 (28)	804 (27)	105 (58)‡
LVEF (%)	56.4 ± 11.9	56.9 ± 11.3	47.6 ± 16.3‡
LVEF <50% (%)	663 (21)	576 (19)	87 (48)‡

Numbers in parentheses refer to the percentage of patients in the column who have the particular variable. *P* values compare these percentages between the event-free and cardiac event columns.
*Ninety patients have missing values.
‡$P < .001$ compared with event-free.
LV, left ventricular; *LVEF*, left ventricular ejection fraction; *MVD*, multivessel disease; *SSS*, summed stress score (perfusion).

Abnormal perfusion images increased the cumulative incidence of both MI, from 1.2% (23/1970) to 3.1% (38/1237) ($P < .001$), and cardiac death, from 2.0% (40/1970) to 6.4% (79/1237) ($P < .001$).

Annual event rates were derived for all patients with time-to-event data (n = 2960). Figure 1 illustrates a steady increase in the annual event rate in relation to the extent and severity of perfusion image abnormalities as measured by the SSS. Patients with abnormal perfusion images had an annual event rate of 5.1% compared with 1.6% for patients with normal images ($P < .001$). Patients with severely abnormal images (SSS ≥6) had a greater than 4-fold increase in the annual incidence of an event: 7.0% versus 1.6% ($P < .001$).

For patients with defects in multiple vascular territories, the annual event rate was 8.6%, significantly higher ($P = .002$) than the rate of 5.1% for the broader group of patients with abnormal images. The presence of reversible left ventricular cavity dilatation increased the event rate to 9.0% ($P = .034$ compared with patients who had abnormal images).

Relationship of ECG-gated SPECT Ventricular Function Measurements to Cardiac Event Rates

The cumulative cardiac event rate was significantly higher in patients with an abnormal wall motion score (≥2) than those with a normal score: 11.6% versus 3.3% ($P < .001$). Similarly, the presence of an abnormal LVEF was associated with a higher cumulative event rate than in patients with normal left ventricular function: 13.1% versus 3.7% ($P < .001$).

The type of cardiac event was examined in relation to ventricular function. The incidence of both MI and cardiac death was increased by abnormal ECG-gated SPECT images. An abnormal wall motion score increased the cumulative incidence of MI from 1.3% (30/2298) to 3.4% (31/909) ($P < .001$) and cardiac death from 2.0% (45/2298) to 8.1% (74/909) ($P < .001$). An abnormal LVEF increased the cumulative incidence of MI from 1.5% (39/2544) to 3.3% (22/663) ($P = .005$) and cardiac death from 2.1% (54/2544) to 9.8% (65/663) ($P < .001$).

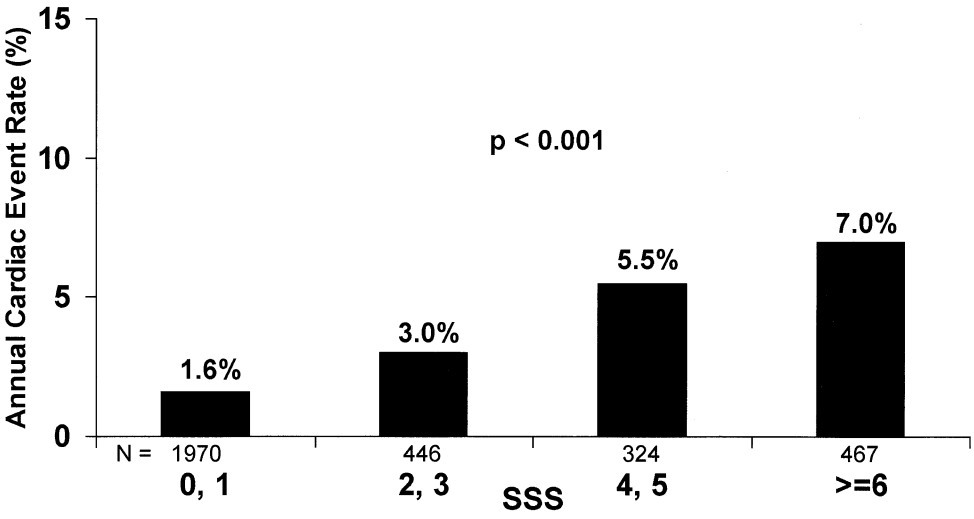

Figure 1. Annual incidence of cardiac events (cardiac death or nonfatal MI) in relation to extent and severity of SPECT perfusion abnormality as measured by SSS (0-1, normal myocardial perfusion; 2-3, mildly abnormal myocardial perfusion; 4-5, moderately abnormal myocardial perfusion; and ≥6, severely abnormal myocardial perfusion).

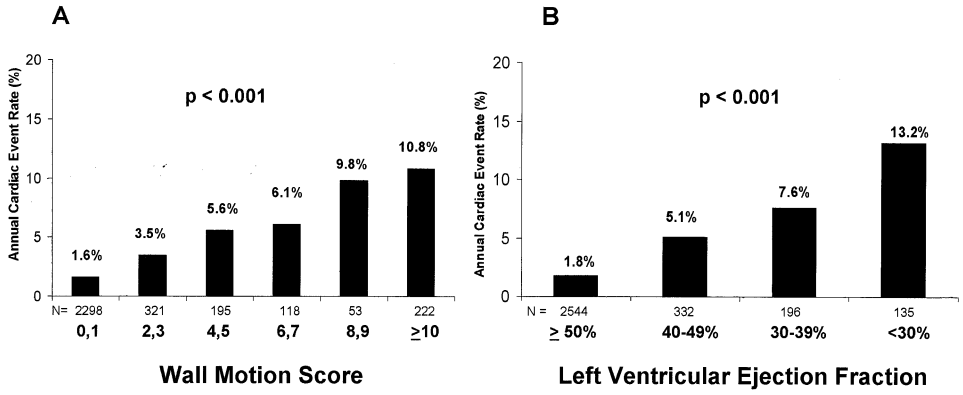

Figure 2. Incidence of cardiac events in relation to ECG-gated SPECT results. **A**, Event rates in relation to wall motion score. **B**, Event rates in relation to LVEF.

The relationship between global function (LVEF) and wall motion score was evaluated. Of 2744 patients with a normal LVEF, 300 (11%) had an abnormal wall motion score, increasing the cumulative event rate from 3.2% to 7.3% ($P < .001$). The cumulative incidence of infarction increased from 1.3% to 3.3% ($P = .014$), and that of cardiac death increased from 1.9% to 4% ($P = .03$).

Figure 2 demonstrates the progressive increases in the annual cardiac event rates as wall motion scores and LVEF worsened. Patients with an abnormal wall motion score had an event rate of 6.1% per year compared with 1.6% per year for those with a normal score ($P < .001$), with a greater than 6-fold increase for a wall motion score of 10 or more. Patients with an abnormal LVEF had an event rate of 7.4% per year compared with 1.8% per year for those with a normal LVEF ($P < .001$), with a greater than 7-fold increase in the event rate for LVEF lower than 30% ($P < .001$).

Incremental Value of Ventricular Function Over Perfusion Data

Left ventricular functional data from ECG-gated SPECT added prognostic information to perfusion image findings, as shown in Figure 3. In the presence of normal perfusion images, an abnormal wall motion score increased the cumulative event incidence from 2.7% (50/1811) to 8.2% (13/159) ($P < .001$), whereas in the presence of abnormal perfusion images, the cumulative event rate increased from 5.1% (25/487) to 12.3% (92/750) ($P < .001$). Similarly, an abnormal LVEF increased the event rates for both normal and abnormal

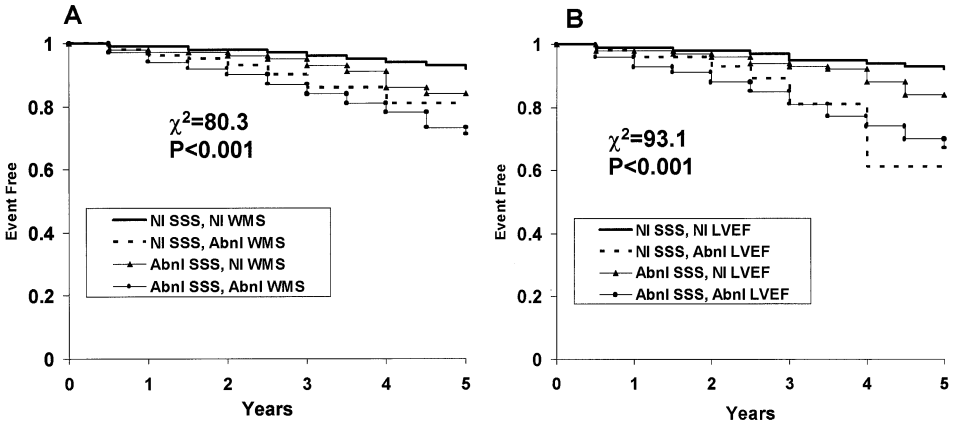

Figure 3. Kaplan-Meier event-free survival curves in relation to SPECT perfusion and ECG-gated SPECT functional results. **A**, Event-free survival in relation to perfusion SSS and wall motion score (*WMS*). The χ^2 test is performed by the method of Tarone-Ware and, with the *P* value, compares all 4 curves. For individual comparisons, the findings were as follows: normal (*Nl*) SSS/Nl WMS versus Nl SSS/abnormal (*Abnl*) WMS, $\chi^2 = 13.2$ and $P < .001$; Abnl SSS/Nl WMS versus Abnl SSS/Abnl WMS, $\chi^2 = 12.9$ and $P < .001$; Nl SSS/Nl WMS versus Abnl SSS/Nl WMS, $\chi^2 = 6.5$ and $P < .011$; and Nl SSS/Abnl WMS versus Abnl SSS/Abnl WMS, $\chi^2 = 1.89$ and $P =$ not significant (.17). **B**, Event-free survival in relation to perfusion SSS and LVEF. The χ^2 test is performed by the method of Tarone-Ware and, with the *P* value, compares all 4 curves. For individual comparisons, the findings were as follows: Nl SSS/Nl LVEF versus Nl SSS/Abnl LVEF, $\chi^2 = 6.5$ and $P = .01$; Abnl SSS/Nl LVEF versus Abnl SSS/Abnl LVEF, $\chi^2 = 22.5$ and $P < .001$; Nl SSS/Nl LVEF versus Abnl SSS/Nl LVEF, $\chi^2 = 7.2$ and $P < .007$; and Nl SSS/Abnl LVEF versus Abnl SSS/Abnl LVEF, $\chi^2 = 1.67$ and $P =$ not significant (.20).

perfusion images: 8.8% (7/80) versus 3.0% (56/1890) ($P = .011$) and 13.7% (80/583) versus 5.6% (37/654) ($P < .001$), respectively.

Cox Regression Analysis

For this analysis, the events of nonfatal MI and cardiac death were considered separately, as previous work has shown that the variables predicting these events differ.[11,24] By Cox regression analysis (Table 3), MI was independently predicted by the presence of diabetes (odds ratio [OR], 2.13; 95% confidence interval [CI], 1.30-3.49), the number of vascular territories with a perfusion defect (OR, 1.58 per vessel; 95% CI, 1.11-2.24), and age (OR, 1.04 per year; 95% CI, 1.01-1.06). No ventricular function variable independently predicted MI by this analysis.

Cardiac death was independently predicted by the use of pharmacologic stress (OR, 6.54; 95% CI, 3.58-11.95), an abnormal ejection fraction (OR, 2.28; 95% CI, 1.44-3.61), male gender (OR, 2.18; 95% CI, 1.45-3.28), hypertension (OR, 2.18; 95% CI, 1.40-3.39), diabetes mellitus (OR, 1.63; 95% CI, 1.10-2.41), the number of vascular territories with a perfusion abnormality (OR, 1.45 per vessel; 95% CI, 1.10-1.91), and age (OR, 1.04 per year; 95% CI, 1.02-1.05).

Using Perfusion Imaging and Ventricular Function Data To Predict Cardiac Death

Given that the number of vascular territories with a defect was the perfusion variable that best predicted cardiac death, it was analyzed with the LVEF and related to the annual cardiac mortality rate (Figure 4). For patients with no perfusion defects, an LVEF of 30% to 49% increased the mortality rate from 0.8% (for LVEF ≥50%) to 4.8% ($P < .001$), with no additional event increase (to 3.4%) for LVEF lower than 30%. For patients with a perfusion defect in one vascular territory, the mortality rate increased from 1.3% (LVEF ≥50%) to 2.5% for an LVEF of 30% to 49% ($P = .07$), with a significant increase to 4.8% for an LVEF lower than 30% ($P < .05$ compared with LVEF ≥50%). Finally, for patients with defects in multiple vascular territories, an LVEF of 30% to 49% increased the cardiac mortality rate from 1.1% (LVEF ≥50%) to 5.8% ($P < .05$), and an LVEF lower than 30% further increased the rate to 11.2% ($P < .001$).

Perfusion imaging data also added value to ventricular function data. For patients with an LVEF of 30% to 49%, defects in multiple vascular territories increased the event rate from 2.5% (for patients with a defect in one vascular territory) to 5.8% ($P < .05$). In patients with an

Table 3. Cox regression analysis

VARIABLE	Nonfatal MI			Cardiac death		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Age (per year)	1.04	1.01–1.06	.001	1.04	1.02–1.05	.000
Male gender	0.69	0.41–1.14	.155	2.18	1.45–3.28	.000
Previous MI	0.87	0.46–1.62	.641	1.11	0.69–1.77	.678
Previous CABG	1.03	0.50–2.13	.93	0.95	0.57–1.60	.859
Previous PCI	1.67	0.85–3.30	.138	0.90	0.49–1.65	.735
Diabetes	2.13	1.30–3.49	.003	1.63	1.11–2.41	.013
Hypertension	1.04	0.64–1.71	.866	2.18	1.40–3.39	.001
Pharmacologic stress	1.28	0.74–2.21	.377	6.54	3.58–11.95	.000
Baseline normal ECG	0.98	0.56–1.70	.93	0.63	0.41–0.97	.035
ECG ischemia	1.13	0.97–1.33	.127	1.11	0.96–1.29	.15
SSS	1.05	0.93–1.18	.419	0.95	0.87–1.04	.238
No. of vascular territories with perfusion defect (per vessel)	1.58	1.11–2.24	.010	1.45	1.10–1.91	.008
Abnormal LVEF	1.31	0.71–2.43	.384	2.28	1.44–3.61	.000

CABG, Coronary artery bypass grafting; *PCI,* percutaneous coronary intervention.

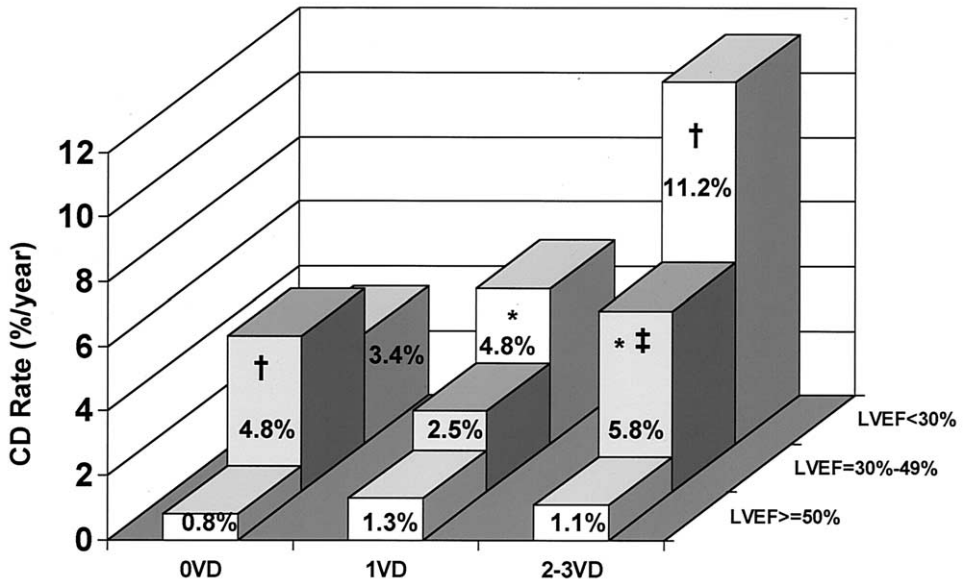

Figure 4. Annual incidence of cardiac death (*CD*) in relation to number of vascular territories with a perfusion defect (*VD*) and LVEF. *$P < .05$ compared with ejection fraction of 50% or greater. †$P < .001$ compared with ejection fraction of 50% or greater. ‡$P < .05$ compared with 1 VD.

LVEF lower than 30%, the presence of perfusion defects increased the event rate from 4.8% (defect in one territory) to 11.2% (multiple defects) but, because of small patient numbers, only achieved a statistical trend ($P = .16$).

DISCUSSION

This study sought to further investigate the ability of functional data from ECG-gated SPECT perfusion imaging to supplement perfusion data in predicting patient

outcomes. We found that abnormal ventricular function predicted an increased incidence of nonfatal MI and cardiac death. Compared with patients with normal ventricular function, those with an LVEF lower than 30% had a greater than 7-fold increased incidence of an event, and those with the most severely abnormal wall motion score had a more than 6-fold increase. Abnormal ECG-gated SPECT results worsened the prognosis for both patients with normal perfusion image results and those with abnormal results. An abnormal LVEF worsened prognosis in patients with a perfusion defect in 0, 1, or 2 to 3 vascular territories. Likewise, for patients with an abnormal LVEF, prognosis most often worsened as the number of territories with a perfusion defect increased, particularly if there was evidence of multivessel disease. Patients with an LVEF lower than 30% and defects in multiple territories had a particularly poor prognosis. These data suggest that both perfusion and ventricular function provide important risk stratification information.

Previous Work With Functional Data From ECG-gated SPECT

At this time, only a few studies have addressed the potential prognostic value of functional data acquired during stress perfusion imaging. Nallamouthu et al,[25] using a first-pass radiotracer technique, found no difference in survival rate between patients with normal LVEF versus those with abnormal LVEF, concluding that ejection fraction adds little prognostic information to perfusion results. In contrast, two recent studies of selected populations found that functional data from ECG-gated SPECT helped to risk-stratify patients with recent MI and those undergoing noncardiac surgery.[26,27] Lima et al[9] reported that using gated SPECT improved the detection of high-risk coronary artery disease.

With regard to a large unselected population, Sharir et al[10] reported that patients with an abnormal ejection fraction on ECG-gated SPECT had a markedly higher cardiac mortality rate (9.2% per year) than patients with a normal ejection fraction (<1% per year) ($P < .00001$). LVEF had incremental prognostic value over prescan and perfusion information. In a subsequent study by this group, the poststress gated SPECT ejection fraction was the best predictor of cardiac death, whereas the amount of ischemia best predicted subsequent MI.[11]

The current study confirms and extends the findings of Sharir et al.[10,11] We found that gated SPECT predicted patient outcome regardless of whether we used a quantitatively derived LVEF or a visual, semiquantitatively derived gated SPECT wall motion score. In the setting of a preserved LVEF, an abnormal wall motion score more than doubled the risk of an event.

Perfusion Imaging and Functional Data From ECG-gated SPECT as Independent Predictive Variables

In contrast to the studies by Sharir et al,[10,11] we found that for patients with a moderately reduced LVEF (30%-49%), the presence of perfusion defects in multiple vascular territories increased the cardiac mortality rate. Similarly, for patients with a severely reduced LVEF (<30%), there was a marked increase in the mortality rate for those with defects in multiple vascular territories, but the low number of patients likely resulted in a failure to achieve statistical significance.

A confounding factor to consider is that sometimes patients with poor ventricular function and no or minimal perfusion abnormalities have a nonischemic-cardiomyopathic component to their coronary disease that increases the risk of death. This possibility may explain the apparent relatively high mortality rate (4.8%) in patients with no perfusion defects and an LVEF of 30% of 49%. The number of patients in this group was low ($n = 56$), suggesting that further studies are needed to confirm these findings.

Significance of Poststress LVEF

In this study all ECG-gated SPECT images were obtained 15 to 60 minutes after stress. As previously shown, this may not accurately reflect resting ventricular function in some patients. Johnson et al[28] demonstrated that the poststress gated SPECT images frequently show worsened ventricular function compared with post-rest gated images. A diminished ejection fraction on the poststress images correlated with the presence of extensive perfusion abnormalities indicative of severe multivessel coronary disease. Recently, Emmett et al[29] demonstrated that a reversible regional wall motion abnormality is often associated with a high-grade stenosis. A proposed mechanism for this phenomenon is poststress myocardial stunning. A reversible regional wall motion abnormality may indicate an area at high risk for infarction and/or a fatal arrhythmia. As such, the prognostic value of ECG-gated SPECT may relate both to baseline ventricular function and to the potential impact of ischemia or infarction on function, making it a particularly powerful predictor of outcome.

MI Versus Cardiac Death as an Outcome

Studies have shown that variables predictive of MI often differ from those that predict cardiac death.[11,20,24] MI usually results from rupture of an atherosclerotic plaque and therefore should be predicted by variables that reflect the extent of atherosclerotic disease, such as

the amount of myocardial ischemia (ie, the number of lesions at risk for rupture).[30] Cardiac death, on the other hand, correlates not only with the extent of atherosclerotic disease, but also with ventricular function, particularly what function would remain after an additional ischemic event.

Our data showed that MI was independently predicted by an ischemic variable—the number of territories with a perfusion defect—as well as by variables that would be associated with more extensive atherosclerosis—age and diabetes. Cardiac death, however, was predicted by variables that reflected the state of ventricular function, such as ejection fraction and the need to undergo pharmacologic stress testing. Separating predictors of MI and cardiac death is important, as MI appears to be best prevented by aggressive medical management whereas the likelihood of cardiac death is often best reduced with revascularization.[31,32]

Importance of Clinical Parameters

Myocardial perfusion and functional studies should be interpreted in conjunction with clinical data. We found diabetes to be a predictor of both MI and cardiac death. Recent studies have consistently shown that the presence of diabetes mellitus indicates a poorer prognosis for any degree of image abnormality.[17,33,34] In addition, asymptomatic patients with diabetes mellitus frequently have abnormalities on perfusion imaging and are likely to be at increased risk of an adverse outcome from their silent disease.[35]

Consistent with previous reports, our data showed that referral for pharmacologic stress testing is an important risk factor in predicting future cardiac event.[20,36] The inability to exercise is not only a potential indicator of poor ventricular function but may indicate other significant co-morbidities, such as peripheral vascular disease or prior stroke, that reflect the overall severity of cardiovascular disease. The large percentage (42%) of patients undergoing pharmacologic stress testing likely accounts for our finding of a higher-than-expected event rate (1.6%) in patients with normal perfusion images.[20]

Limitations

Current investigative studies examining the prognostic value of stress perfusion imaging are limited by the referral of patients with more severely abnormal test results to more aggressive management (ie, revascularization). This “management referral bias” often results in a relatively low-risk subpopulation remaining for follow-up. In some instances the remaining patients are relatively healthy, but in other cases this cohort contains patients deemed too ill to be referred for revascularization. In this study, patients referred for early revascularization had substantially more perfusion and gated SPECT abnormalities than those remaining for follow-up. Despite this potential problem, our results are in accord with published literature.

The follow-up rate in this study was high (>91%). There is a concern that patients lost to follow-up may have disproportionately higher event rates. Nevertheless, in our cohort, patients lost to follow-up appeared to be healthier, being younger with less previous cardiac history and less extensive and severe perfusion abnormalities, making a higher event rate unlikely.

This study used an 8-segment model for perfusion image interpretation, as the data were collected before publication and acceptance of current recommendations to use a 17-segment model.[19] Nevertheless, our result patterns (if not the exact numbers) are consistent with published literature. A recent suggestion that determining the percentage of myocardial involvement may be a better method by which to semiquantitatively assess SPECT perfusion images may allow comparison of studies that use different scoring techniques.[37]

Conclusions

Functional data from ECG-gated SPECT add important prognostic information to stress myocardial perfusion imaging. Both perfusion and functional data provide independent power, adding to key clinical variables. ECG-gated SPECT should routinely be performed, reported with all stress perfusion image studies, and incorporated into risk assessment.

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